ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 41, NO. 5 NOVEMBER, 1954

Contents

	Page
Endemic Goiter: A Problem in Preventive Medicine. David Marine	875
Periarteritis Nodosa: Recognition and Clinical Symptoms. M. A. Blankenhorn and Harvey C. Knowles, Jr.	887
Osteomalacia in New York. I. Snapper, R. Seely, S. Falk and I. Feder	893
The Relation of Physical Activity and Occupation to Coronary Artery Heart Disease. Joseph G. Benton and Howard A. Rusk	910
The Electrocardiogram in the Examination of the Industrial Worker. J. Richard Durham and Lemuel C. McGee	918
Factors Concerned in the Genesis of Cardiac Arrhythmias. Alfred M. Wood and Stephen M. Tenney	935
The Selective Use of Anticoagulants in Acute Myocardial Infarction Based on Initial Prognosis. Morton M. Halpern, Louis Lemberg, Martin Bella and Herbert Eichert	942
Persistent Nonhemolytic Hyperbilirubinemia Associated with Lipochrome-Like Pigment in Liver Cells: Report of Four Cases. Helmuth Sprinz and Robert S. Nelson	952
Occurrence of Accumulation of Fat in the Liver and Its Relation to Excess Weight Gain in Patients Convalescing From Viral Hepatitis. Arthur R. Colwell, Jr.	963
Pulmonary Function in Mitral Stenosis: A Review of Current Concepts. Ralph C. Scott	980
Pulmonary Arteriovenous Fistula and Telangiectasia. Eugene Weiss and Benjamin M. Gasul	989
Scleroderma (Based on a Study of Over 150 Cases). Irving Leinwand, A. Wilbur Duryee and Maurice N. Richter	1003
Case Reports:	
Hereditary Hemorrhagic Telangiectasia: A Report of Pulmonary Arteriovenous Fistulae in Mother and Son; Medical (Hormonal) and Surgical Therapy of This Disease. Edward C. Heyde	1042
Hereditary Unilateral Hydronephrosis. J. Floyd Cannon	1054
False-Positive Reaction to the Regitine Test for Pheochromocytoma. Ralph D. Ross	1061
Whipple's Disease (Intestinal Lipodystrophy): Review of the Literature and Report of a Case Successfully Treated with Adrenocorticotropin (ACTH) and Cortisone. Jerome Radding and Marshall J. Fiese	1066
Phenylbutazone Toxicity: Report of a Case of Acute Renal Failure. Mortimer B. Lipsett and Ralph Goldman	1073
Hypertension Associated with Renal Neoplasm: Report of Two Cases. Robert M. Dowben	1079
Editorial—Transmissibility of Leukemia	1084
Reviews	1089
College News Notes	1094

THIRTY-SIXTH ANNUAL SESSION—PHILADELPHIA, PA., APRIL 25-29, 1955

PEPTIC ULCER:

PAIN PATTERNS, DIAGNOSIS AND MEDICAL TREATMENT

By LUCIAN A. SMITH, M.D., Mayo Clinic and Foundation
and ANDREW B. RIVERS, M.D., Late, Mayo Clinic and Foundation
with Foreword by GEORGE B. EUSTERMAN, M.D.

This book presents the latest tested methods for the precise diagnosis and satisfactory medical management and treatment of the peptic ulcer. It is unique in its emphasis on careful clinical evaluation of specific diagnostic pain patterns, methods for the prevention of recurrence, and an educational form of therapy which leads to full cooperation by the patient in resuming daily activities with frequently lasting comfort. The illustrative material is most valuable.

1ST EDITION. JULY 1953. 575 PAGES. 210 ILLUS. $12.50

LEGAL MEDICINE, PATHOLOGY AND TOXICOLOGY

By THOMAS A. GONZALES, M.D., MORGAN VANCE, M.D.
and MILTON HELPERN, M.D., with CHAS. J. UMBERGER, Ph.D.

This is a completely rewritten and enlarged text for physicians concerned with the many medicolegal problems involved in deaths (approx. 300,000 yearly) resulting from violence or obscure causes. Sections on clinical and analytic toxicology are of great value. 658 original illustrations supplement the text.

2ND EDITION. AUG. 1954. 1370 PAGES. 658 ILLUSTRATIONS. $22.00

HOLT PEDIATRICS

By L. EMMETT HOLT, JR., M.D. and RUSTIN McINTOSH, M.D.
with 72 Collaborating Authorities

This completely rewritten and modernized twelfth edition covers the entire wide range of pediatric practice and teaching. It is authoritative, clearly written, fully documented and well-balanced. Actually, it is a definitive textbook of medicine as applied to the age group which includes children from birth through puberty. In the words of one reviewer, "The book is almost as up to date as last month's medical journals. New fields, such as the uses of ACTH and cortisone, the chemotherapy of tuberculosis, the latest antibiotics, and modern pediatric surgery, are set forth clearly and at reasonable length."

12TH EDITION. AUG. 1953. 1303 PAGES. 263 ILLUS. $15.00

THE UNIPOLAR ELECTROCARDIOGRAM

By JOSEPH M. BARKER, M.D., Georgetown Univ.
with JOSEPH J. WALLACE, M.D., and WALLACE M. YATER, M.D.
and Foreword by FRANK N. WILSON, M.D.

This practical text is a complete and easily understood coverage of the basic principles, established facts and correct interpretation of the electrocardiogram for correlation with the history, physical findings and other tests in the diagnosis of heart disease or functional impairment. Illustrative diagrams are supplemented by complete, instructive legends. Reproduced tracings include single strips, the three standard limb leads, extremity leads and precordial leads. Serial reproductions from actual cases show the progressive or regressive nature of various conditions. The cardiac arrhythmias are covered fully.

1ST EDITION. JUNE 1952. 667 PAGES. 458 ILLUS. $12.50

APPLETON-CENTURY-CROFTS, INC.

(Publishers of THE NEW CENTURY CYCLOPEDIA OF NAMES)

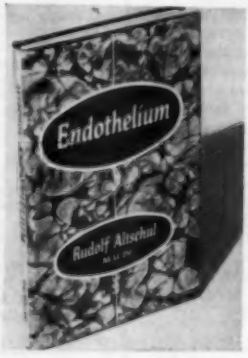
35 WEST 32nd STREET, NEW YORK 1, N. Y.

Subscription per annum, net postpaid, $10.00, United States, Canada, Hawaii, and Puerto Rico; $11.00, other countries.

Entered as Second Class Matter August 31, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1950.

ENDOTHELIUM: ITS DEVELOPMENT, MORPHOLOGY, FUNCTION, AND PATHOLOGY

It was not for the sake of pure science alone that Dr. Rudolf Altschul, Professor of Histology at the University of Saskatchewan, delved into the facts pertaining to the endothelium. In fact, he was virtually driven to his inquiry into pure science simply by attempting to investigate problems of arteriosclerosis and other vascular disease.

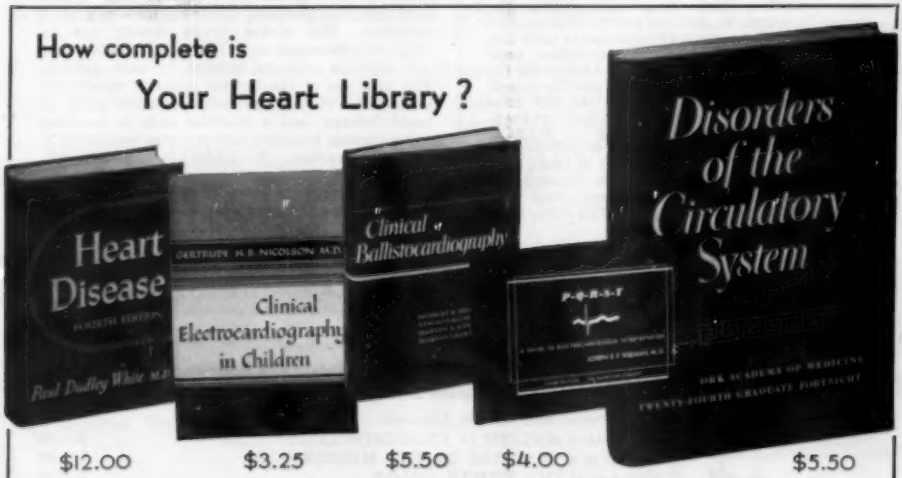


Prompted by the hard facts of statistical data, i.e. that the largest number of natural deaths from a single cause in North America is ascribed to cardiovascular disease, he felt a definite need for exploration of the available information on endothelial tissue. The fruits of his exhaustive research, and of his own interpretive contribution, are now available in book form. (*Endothelium: Its Development, Morphology, Function, and Pathology*, The Macmillan Company, 60 Fifth Avenue, New York, probable price $3.50.)

Contains all the information pertaining to endothelium that was available to the author. After covering every aspect of development, morphology, and physiology of the endothelium, the book brings into focus specific aspects of its pathology.

Dr. Altschul's book is an outstanding contribution to medical knowledge; it should find wide acceptance in medical schools and will prove of special interest to internists and, more particularly, to practitioners in the cardiovascular and geriatrics fields.

How complete is
Your Heart Library?



$12.00 $3.25 $5.50 $4.00 $5.50

The Macmillan Company
60 FIFTH AVENUE, NEW YORK 11, N. Y.

Hoeber-Harper H|H Text Books

PASCHKIS, RAKOFF & CANTAROW'S

CLINICAL ENDOCRINOLOGY

Outstanding! Here is the first complete and integrated account of the endocrine system, its disorders and its relation to the rest of the body. Based on understanding endocrinopathies as problems in pathologic physiology, it gives you a rational guide to diagnosis and treatment in your own practice. In this single source-book *every* phase of endocrinology is at your fingertips. No topic has been slighted in an effort to provide a complete clinical guide. And, because the authors work and teach together the book has a unity of thought and concept. By KARL E. PASCHKIS, M.D., *Assoc. Prof. of Physiology*, ABRAHAM E. RAKOFF, M.D., *Clin. Prof. of Obstet. & Gynec. Endocrinol.* & ABRAHAM CANTAROW, M.D., *Prof. of Biochem., All of Jefferson Med. Coll.*, 860 pp., 253 illus., 5 in full color, $16.00.

ADAMS, DENNY-BROWN & PEARSON'S

DISEASES OF THE MUSCLE

A Study in Pathology. This is the first monograph on muscle diseases to appear in English, and the first in any language for decades. Opening with detailed descriptions of structure and formation of muscle, the second half is devoted to pathologic changes which may occur. Clinical and pathologic findings are correlated in an effort to reach an integrated concept of the mechanism of muscle diseases. Finally, methods for biopsy, autopsy and staining rounds out the book for practical use. Extremely useful for the neurologist and the pathologist, as well as the surgeon, the internist, the orthopedist and the pediatrician. By RAYMOND D. ADAMS, M.D., *Assoc. Clinical Prof. of Neurology, Harvard Medical School*, D. DENNY-BROWN, M.D., *James Jackson Putnam Prof. of Neurology, Harvard Medical School* & CARL M. PEARSON, M.D., *Former Resident in Pathology, Mallory Institute of Pathology, Boston City Hospital*, 571 pp., 330 illus., 1953, $16.00.

GRACE, WOLF & WOLFF'S

THE HUMAN COLON

New Light on Colonic Function. This unique study of four patients with exposed segments of colon describes from direct observation the changes in colonic appearance and function accompanying normal reactions experienced in daily life, such as anger, fear, satisfaction, dejection, pain, etc. Many important conclusions emerge on the relation between the emotional life and the colonic functions of a given personality. 31 full color illustrations vividly reveal the colonic changes under discussion. By WILLIAM J. GRACE, M.D., *Asst. Prof. of Medicine*, STEWART WOLF, M.D., *Assoc. Prof. of Medicine* & HAROLD G. WOLFF, M.D., *Prof. of Medicine (Neurology), all at Cornell Univ. Medical College, New York Hospital.*, 260 pp., 112 illus., 31 in full color, 1951, $7.50.

STEWART'S

CARDIAC THERAPY

Completely Practical! Describing in the greatest detail what to do for your cardiac patient, this book gives the accepted treatment for every heart condition. The author shows clearly how to adapt this treatment to fit the problem before you and build a regimen tailored to each patient. The safe use of the newest drugs is specifically explained. This is the most complete guide to heart therapy, and a practical help in handling every cardiac condition that you may encounter in everyday practice. By HAROLD J. STEWART, M.D., F.A.C.P., *Assoc. Professor of Medicine, Cornell, Head of Div. of Cardiology, New York Hosp.*, 630 pp., 73 illus., 1952, 2nd printing 1953, $10.00.

ANY HOEBER-HARPER BOOK SENT ON APPROVAL

H|H

Use This Handy Order Form Today

PAUL B. HOEBER, INC. AIM 1154

Medical Book Department of Harper and Brothers

49 East 33rd Street, New York 16, New York

Please send me *On Approval:*

- ☐ Paschkis et al CLINICAL ENDOCRINOLOGY $16.00
- ☐ Adams et al DISEASES OF THE MUSCLE $16.00
- ☐ Grace et al THE HUMAN COLON ..... $ 7.50
- ☐ Stewart's CARDIAC THERAPY $10.00

☐ Check Enclosed (return privileges, of course) ☐ Bill Me

Name .....

Address .....

City ..... Zone ..... State .....

Please Mention this Journal when writing to Advertisers

HELPFUL BOOKS FOR A BUSY INTERNIST

New! — Albritton's Standard Values in Nutrition and Metabolism

160 fact-packed tables make up this useful new book. They cover vitamins, "growth factors," food composition, functions of each nutrient and signs and symptoms of their deficiency or excess, basal and resting metabolic rates, etc.

Edited by Everett C. Albritton, A.B., M.D., Fry Professor of Physiology, George Washington University. Prepared under the Direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, National Academy of Sciences—The National Research Council. 380 pages, 8½" x 11". $6.50. *New!*

New (4th) Edition! — Andrews' Diseases of the Skin

Brings you the latest advances in the field—including help on the L. E. phenomenon, and skin manifestations of internal cancer.

By George Clinton Andrews, M.D., F.A.C.P., Clinical Professor of Dermatology, the College of Physicians and Surgeons, Columbia University. 877 pages, 6" x 9", with 777 illustrations. $13.00. *New (4th) Edition!*

AIM 11-54

W. B. SAUNDERS COMPANY, West Washington Square, Philadelphia 5

Send me the following and charge my account: ☐ Easy Payment Plan

☐ Albritton's Standard Values in Nutrition & Metabolism..... $6.50

☐ Andrews' Diseases of the Skin..... 13.00

Name.....

Address.....

New 2nd Edition

Moritz—The Pathology of Trauma

By Alan Richards Moritz, M.D.

Professor of Pathology and Director of the Institute of Pathology, School of Medicine, Western Reserve University, Cleveland, Ohio.

Dr. Moritz surveys the leading causes of injuries produced by violence, including those caused by industrial accidents and war. The enlarged *new 2nd edition* contains a new chapter on medicolegal autopsy, a new discussion of the psychosomatic complication of trauma, and a summary of post-traumatic systemic metabolic disturbances that constitute the general adaptation syndrome. Other subjects which are new or rewritten include injuries of the central nervous system and of the urogenital tract, trauma and infection, injuries due to high explosives, mechanisms and complications of secondary shock, trauma and heart failure, respiratory tract injuries, and other important data.

New 2nd Edition. 414 Pages. 126 Illustrations. $8.50

New Book

Forsee—The Surgery of Pulmonary Tuberculosis

By James H. Forsee, A.B., B.S., M.D., F.A.C.S., F.A.C.P.

Colonel, M. C., U. S. Army; Chief, Surgical Services, Fitzsimons Army Hospital, Denver, Colorado.

From an extensive experience, supplemented by an abundance of clinical material from the Fitzsimons Army Hospital, Dr. Forsee has written an authoritative presentation of the advances in surgery of pulmonary tuberculosis since the advent of streptomycin and other antibiotics. The text is divided into three sections: Principles in the Application of Surgery in Pulmonary Tuberculosis; Operative Surgical Procedures; and Experience with Surgical Therapy in Pulmonary Tuberculosis. Phthisiologists and internists will detect a surgical approach which stresses medical aspects and essentiality of the mutual efforts of surgery and medicine to further improve the therapy of pulmonary tuberculosis.

New Book. 208 Pages. 59 Illustrations, 1 in Color. 11 Graphs. 46 Tables. $6.50

Washington Square **LEA & FEBIGER** Philadelphia 6, Pa.

recommended dosage

for pernicious anemia and all treatable anemias

Pronemia*

Vitamin B_{12} • Iron • C • Stomach • Folic Acid • Purified Intrinsic Factor Concentrate

a new and potent oral hematinic • one capsule daily meets the needs of the average patient

Formula contains all known essential hemopoietic factors:

Purified Intrinsic Factor Concentrate	10 mg.	Ferrous Sulfate Exsiccated	400 mg.
Vitamin B_{12}	30 mcg.	Ascorbic Acid (C)	150 mg.
Powdered Stomach	200 mg.	Folic Acid	4 mg.

Lederle

LEDERLE LABORATORIES DIVISION AMERICAN Cyanamid COMPANY Pearl River, N. Y. *REG. U.S. PAT. OFF.

The Williams & Wilkins Co.

Symposium on Sedative & Hypnotic Drugs

Held under the auspices of the Miles-Ames and Sumner Research Laboratories, Elkhart, Indiana

This stimulating treatment of a topic of current importance opens up pathways for future scientific progress in the field. The program of lectures delivered by experts includes:

1. A Neural Basis for the Anesthetic State
2. Enzymes and the Mode of Action of Sedative and Hypnotic Drugs
3. The Relation of the Chemical Sources of sedative and Hypnotic Drugs to their Activity
4. The Pharmacological Evaluation of Sedative and Hypnotic Drugs
5. The Problem of the Clinical Evaluation of Sedative and Hypnotic Drugs
6. Panel Discussion on Clinical Evaluation and Usefulness

150 pp. 25 figs. $3.50

Manson's Tropical Diseases

Edited by
Sir Philip H. Manson-Bahr, F.R.C.P.

The 14th edition of this medical classic includes new chapters on the antibiotics and more space on insecticides. Two new diseases, kwashiorkor and epidemic hemorrhagic fever, are discussed.

Contents include sections on fevers; avitaminoses; abdominal diseases; diseases of the central nervous system; tropical venereal and skin diseases; local diseases; animal parasites; diseases due to poisons; preparation for life in the tropics; insecticides; drugs.

1080 pp. 412 figs. 8 maps
26 plates 29 charts $12.50

THE WILLIAMS & WILKINS COMPANY
Mt. Royal and Guilford Aves. Baltimore 2, Md.

Please Mention this Journal when writing to Advertisers

NEW EDITIONS

Davidson: PRACTICAL MANUAL OF DISEASES OF THE CHEST

Fourth Edition 1954 657 Pages 255 Illustrations $19.25

Fundamentals principles for which this book is justly celebrated have not been sacrificed to provide for the inclusion of new material. It will be found to be now, as it has been for eighteen years, the most complete clinical and pathological survey of chest diseases in the language.

Brock: ANATOMY OF THE BRONCHIAL TREE

Second Edition 1954 275 Pages 157 Illustrations (Many color) $11.00

A remarkable study of bronchial anatomy completely revised and brought up to date.

Frantz and Harvey: INTRODUCTION TO SURGERY

Third Edition 1954 248 Pages 13 Figures $4.00

Fundamental facts have been gathered together with emphasis on basic principles.

Christian, Friend, Schnitker: MEDICAL TREATMENT OF DISEASE

1953 985 Pages Loose-leaf Binding $25.00

A new approach to all who desire to keep abreast of present-day developments in modern therapeutics.

OXFORD UNIVERSITY PRESS, INC., 114 Fifth Ave., New York 11, N.Y.

GOOD FOR GRANDMA, TOO!

Borcherdt

MALT SOUP Extract*

A New Dietary Management for

CONSTIPATED ELDERLY

A bowel content modifier that softens dry, hard stools by dietary means without side effects.[1] Acts by promoting an abundant fermentative bacteria in the colon, thus producing soft, easily evacuated stools. Retards growth of putrefactive organisms. By maintaining a favorable intestinal flora, Malt Soup Extract provides *corrective therapy for the colon, too!*

DOSE: 2 tablespoonfuls b.i.d. until stools are soft (may take several days), then 1 or 2 Tbs. at bedtime.

*Specially processed malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

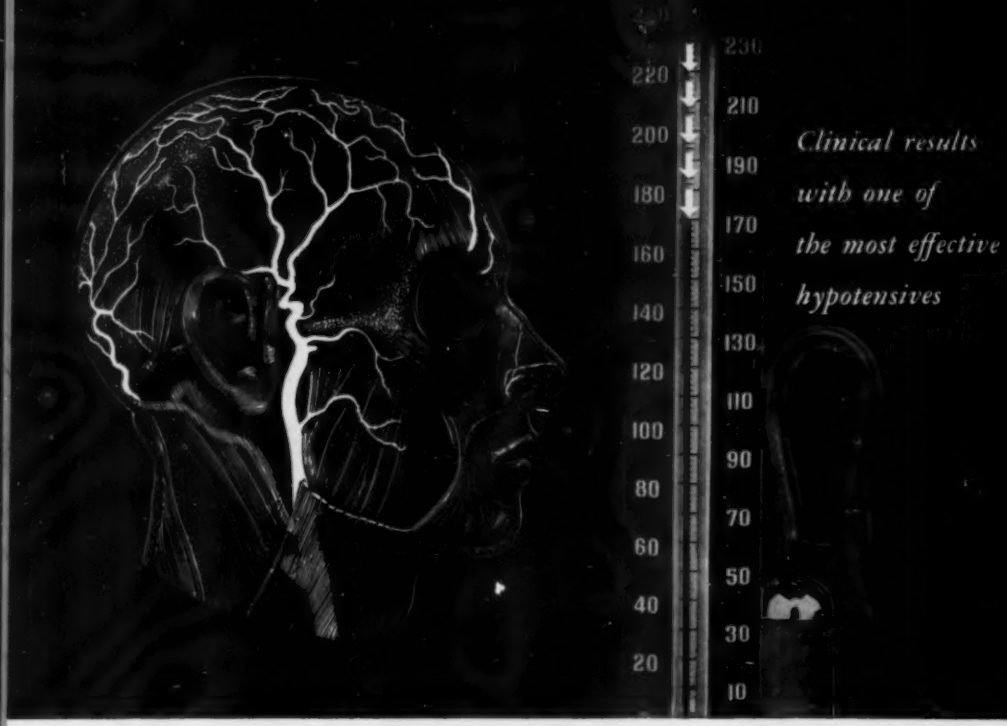
1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation. Journal-Lancet, 73:414 (Oct.) 1953.

Send for Sample

BORCHERDT MALT EXTRACT CO.

217 N. Wolcott Ave. • Chicago 12, Ill.

Please Mention this Journal when writing to Advertisers



Clinical results with one of the most effective hypotensives

Improvement in 79% of patients with hypertensive headache[1]

In addition to the desired reductions in excessive blood pressure in an average of 80 per cent of patients,[1,2] Methium therapy may result in striking relief of the ominous and disabling headaches common to hypertension.[1] For example, headache was relieved in 30 of 38 patients in one study involving 120 hexamethonium-treated patients.[1]

With continued management, up to or beyond a year, blood pressure has been reduced and stabilized, and cardinal symptoms arrested or reversed, without any increase in dosage.[1]

As blood pressure is reduced, and even without reduction, hypertension symptoms have regressed. Retinopathy may disappear; headache, cardiac failure and kidney function may improve.

Methium, a potent autonomic ganglionic blocking agent, reduces blood pressure by interrupting nerve impulses responsible for vasoconstriction. Because of its potency, careful use is required. Pretreatment patient-evaluation should be thorough. Special care is needed in impaired renal function, coronary disease and existing or threatened cerebral vascular accidents.

Literature and samples will be sent promptly if requested.

References:

1. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.

Methium® CHLORIDE

(BRAND OF HEXAMETHONIUM CHLORIDE)

WARNER-CHILCOTT

Mead Johnson and Company

announces its annual

Awards for Graduate Training in Internal Medicine

Continuing progress in American medicine depends on how well today's students, interns and residents are fitted for their challenging tasks. Every possible means of developing their skills and knowledge must be pursued.

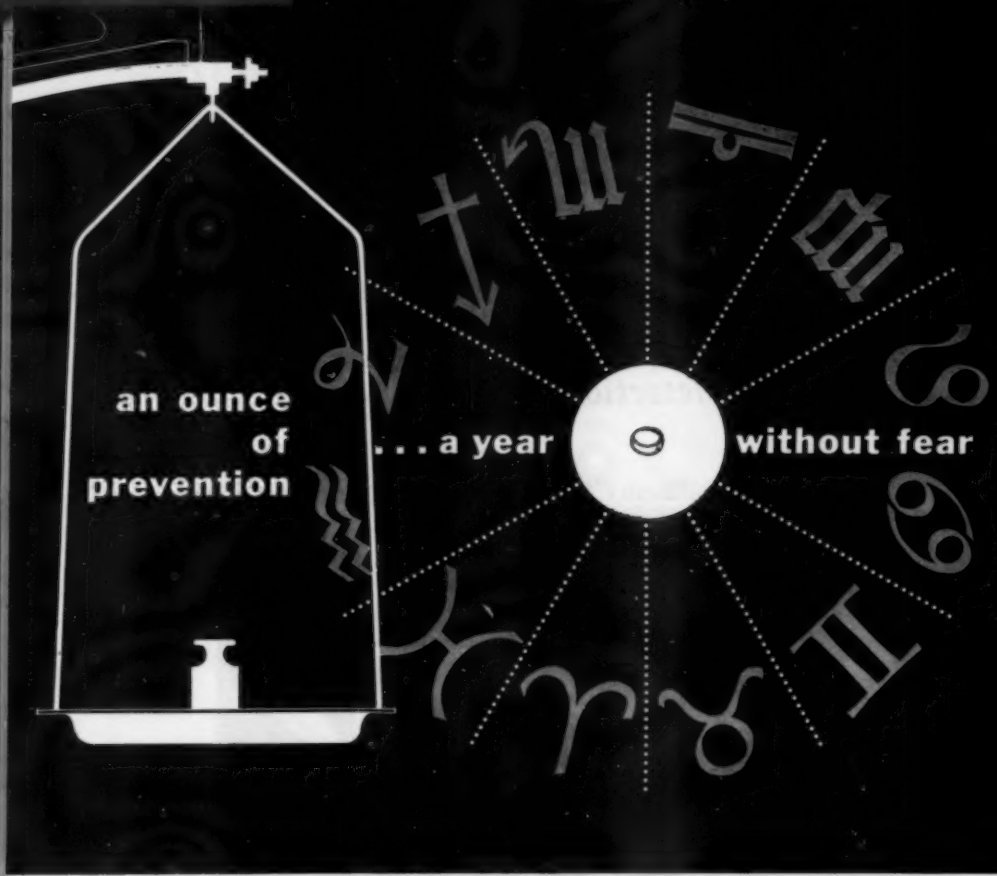
In this spirit, the annual Mead Johnson & Company Awards for Graduate Training in Internal Medicine are made available. The awards make possible an additional year of residency training for the recipients.

The Committee on Fellowships and Awards of the American College of Physicians selects the candidates and administers the funds. As with all its Scholarship Awards, the role of Mead Johnson & Company is limited solely to the provision of funds.

Mead Johnson & Company considers it an honor to play even a small part in the over-all program devoted to developing tomorrow's leaders in medicine.

MEAD JOHNSON & COMPANY

EVANSVILLE, INDIANA, U.S.A.



for the patient with angina pectoris

With Peritrate, the long-acting coronary vasodilator, an ounce of prevention (28,350 mg. of Peritrate) lasts a full year or longer, since only 10 or 20 mg. are needed to protect most patients for 4 to 5 hours. Yet, no arithmetic formula can adequately define the effectiveness of Peritrate in providing dramatic relief from pain and from the fear of anginal attacks.

According to tests made by Russek and coworkers, Peritrate is unexcelled in exerting a prolonged prophylactic effect in angina pectoris. The results achieved ". . . were comparable to those obtained with glyceryl trinitrate (nitroglycerin), but the duration of action was considerably more prolonged."[1] Patients on Peritrate generally exhibit significant EKG improvement,[1,2] and their need for nitroglycerin is often reduced.[3] A continuing year-round schedule of 10 or 20 mg. 4 times a day will usually:

1. reduce the number of attacks (in 8 out of 10 patients[2,3]);
2. reduce the severity of attacks not prevented.

Available in both 10 mg. and 20 mg. tablets and, for extended night-long protection, in Enteric Coated tablets (10 mg.).

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

Peritrate®

tetranitrate

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT

accuracy every time

Clinitest®

BRAND

for detection of urine-sugar

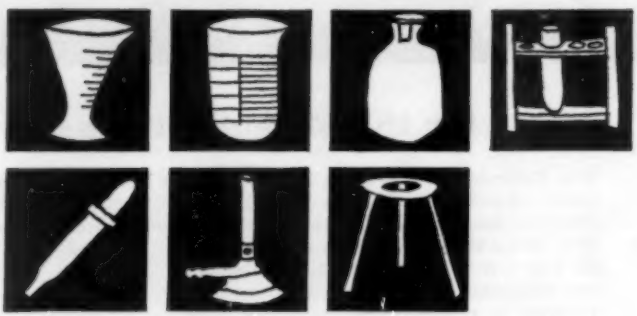
"Both *Clinitest* and Benedict's qualitative test are completely accurate when properly performed."[1]

but

"...there are fewer sources of error with *Clinitest*."[1]

and

"The routine Benedict test...is seldom well performed because of the difficulties of accurate measurement of reagent and urine and because of the practical difficulties of uniform heating; the much simpler and more readily standardized tablet test is to be preferred..."[2]



1. Cook, M. H.; Free, A. H., and Giordano, A. S.: Am. J. M. Technol. *19*:283, 1953.
2. Gray, C. H., and Millar, H. R.: Brit. M. J. *4824*:1361 (June 20) 1953.

Ames Diagnostics—Adjuncts in clinical management

AMES

COMPANY, INC • ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

53254

use FURADANTIN first...

IN URINARY TRACT INFECTIONS

for rapid clearing of the urine

In 30 minutes: antibacterial concentrations in the urine

In 24 hours: the urine is frequently clear

In 3 to 5 days: complete clearing of pus cells from the urine

In 7 days: sterilization of the urine in the majority of cases

With Furadantin there is no proctitis, pruritus ani, or crystalluria.

Average adult dosage: Four 100 mg. tablets daily, taken with meals and with food or milk before retiring.

50 and 100 mg. tablets.

Oral Suspension, 5 mg. per cc.

EATON LABORATORIES
NORWICH, NEW YORK

FURADANTIN®
brand of nitrofurantoin, Eaton

Ann Woodward
Director

You Can't Be Twins—

But you can extend the benefits of your skill and experience without extending yourself beyond reasonable limits. Many other busy physicians have demonstrated the success of the plan which you, also, may desire to adopt: delegate some of your responsibilities to an associate whom you have (1) carefully selected; (2) proved competent by thorough induction into your methods.

The Woodward Bureau gives swift, systematic service in helping physicians to find associates who measure up. Many fine men in all fields of medicine announce their availability through our channels, and our background of over fifty years in professional placement has alerted us to careful interpretations of individual needs.

Whether your requirements are on a permanent or temporary basis, we are prepared to assist you fully.

OUR 58th YEAR
WOODWARD
Medical Personnel Bureau
FORMERLY AINOE'S
• 3RD FLOOR • 185 N. WABASH • CHICAGO 1 •

Formerly the continuing service to the medical profession serving medicine with distinction over half a century

UNIVERSITY OF PENNSYLVANIA
GRADUATE SCHOOL OF MEDICINE

CARDIOLOGY

An eight month full time basic course in cardiology and cardiovascular diseases

•

Beginning September 26, 1955

•

For information address:

The Dean, Graduate School of Medicine, Room 238
UNIVERSITY OF PENNSYLVANIA
Philadelphia 4, Pa.

Pamin

REGISTERED TRADEMARK FOR THE UPJOHN BRAND OF METHSCOPOLAMINE BROMIDE

THE
MEDICAL
PROTECTIVE
COMPANY
FORT WAYNE,
INDIANA
PROFESSIONAL PROTECTION
EXCLUSIVELY
SINCE 1899
specialized service
assures "know-how"

The List of Hospitals Using
SOUTHEY-LEECH TUBES*
for the Rapid and Safe Relief of
MASSIVE EDEMA
Is Impressive
DON'T WAIT UNTIL THE NEED IS IMPERATIVE.
HAVE THEM ON HAND
*Fiese, M. J., and Thayer, J. M.: Archives, Int. Med. 85:132 (Jan. 1950)
Tubes and trocar made of rust-resistant, silver-nickel. Will last indefinitely. Order a set to have on hand. Ask your hospital to keep them on hand.
The Briggs Company
82 WATERMAN ST.
PROVIDENCE 6, RHODE ISLAND
- - Prepare for that emergency—Clip Coupon Now - -
Please send ____ sets of Southey-Leech Tubes, complete with trocar and drainage tubing at $20.00 per set to:
Name:
Street:
City:

Ulcer protection that lasts all night
Pamine
BROMIDE
Tablets • Syrup
Pamine
BROMIDE
with Phenobarbital
Tablets • Elixir • Drops
Upjohn
The Upjohn Company
Kalamazoo, Michigan

Note the Nutritional Difference

THE superior nutritive value of enriched bread over unenriched bread is emphasized by analytical data recently published by the United States Department of Agriculture.[1] Comparison of the two kinds of bread indicates how much more effectively enriched bread contributes to nutritional needs.

Since enriched breads represent an estimated 85 per cent of all commercially produced bread, the evidence shows that bread enrichment has notably increased the B vitamin and iron intake of our population. For this reason enriched bread, since 1941 (when it was first marketed), has been a valuable aid in reducing the incidence of attributable deficiency diseases.[3,4]

But enriched bread contributes to good nutrition in other ways, too. The 13 grams of protein supplied by 5½ ounces (estimated average daily consumption) aids notably in the satisfaction of the daily protein requirement. Since virtually all enriched bread today contains substantial amounts of nonfat milk solids, its protein —consisting of flour and milk proteins—is biologically effective for growth as well as tissue maintenance.

Because of its high nutrient value, its easy and almost complete digestibility, and its universally accepted pleasant, bland taste, enriched bread merits a prominent place not only in the general diet, but in special diets as well. In many reducing diets 3 or more slices daily are included. The average slice of machine-sliced enriched bread supplies only 63 calories.

At notably low cost, enriched bread is making a valuable contribution to the nutritional health of the American people.

1. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared, United States Department of Agriculture, Agricultural Handbook no. 8, 1950.
2. Data furnished by the Laboratories of The American Institute of Baking, Chicago, Illinois.
3. Sebrell, W.H., Jr.: Trends and Needs in Nutrition, J.A.M.A. *152*:42 (May 2) 1953.
4. Flour and Bread Enrichment, 1949-50, The Committee on Cereals, Food and Nutrition Board, National Research Council, 1950.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

B VITAMIN AND IRON CONTRIBUTION OF 5½ OUNCES* OF ENRICHED AND UNENRICHED BREADS AND PERCENTAGES OF RECOMMENDED DAILY ALLOWANCES**

	ENRICHED BREAD		UNENRICHED BREAD (of former years)	
	Amounts	Percentages of Recommended Daily Allowances	Amounts	Percentages of Recommended Daily Allowances
THIAMINE	0.37 mg.	25%	0.08 mg.	5%
NIACIN	3.40 mg.	23%	1.40 mg.	9%
RIBOFLAVIN	0.23 mg.	14%	0.09 mg.	6%
IRON	4.10 mg.	34%	1.10 mg.	9%

*An estimated amount of bread consumed daily by the average person.
**Daily dietary allowances (1953) recommended by the National Research Council for a fairly active man 45 years of age, 67 inches in height, and weighing 143 pounds.

AMERICAN BAKERS ASSOCIATION 20 NORTH WACKER DRIVE, CHICAGO 6, ILL.

in
rheumatoid
arthritis

adrenocortical hormone therapy can transform virtual helplessness into active ambulation

Cortril

tablets

brand of hydrocortisone

when dosage is adjusted to patient's minimum need, Cortril therapy is as safe as therapy with any modern dramatic agent

available as scored tablets, 10 mg. and 20 mg.

also available

TERRA-CORTRIL* Topical Ointment
TERRA-CORTRIL* Ophthalmic Suspension
New, easier-to-write, easier-to-remember names

CORTRIL Topical Ointment

CORTRIL Acetate Ophthalmic Ointment

CORTRIL Acetate Aqueous Suspension for intra-articular injection

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N.Y.

*brand of oxytetracycline and hydrocortisone

IN CANCER PATIENTS

THORAZINE*

—*relieves:*

intractable pain

by the potentiation of analgesics, narcotics and sedatives.

nausea and vomiting

due either to the malignancy or distress-producing therapy.

apprehension and anxiety

associated with cancer and thus promotes a sense of well-being.

From a study of 'Thorazine' in patients with far advanced cancer, Lucas et al. state:

"Favorable effects included relief of pain, muscle spasm, nausea, vomiting, dyspnea, cough, restlessness, apprehension . . . improvement in appetite, sleeping, strength, sense of well-being and decrease in need for narcotics."

Proc. Am. A. Cancer Research *1* 30 (April) 1954

Available in 10 mg., 25 mg. and 50 mg. tablets; 25 mg. ampuls (1 cc.) and 50 mg. ampuls (2 cc.).

Additional information on 'Thorazine' is available on request.

Smith, Kline & French Laboratories

1530 Spring Garden Street, Philadelphia 1

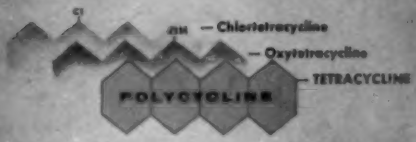
★Trademark for S.K.F.'s brand of chlorpromazine hydrochloride

Chemically it is 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride.

Thoroughbreds are born, not made—

FROM A PRINT "HONORS EVEN" BY EDWIN MEGARGEE. NEW YORK. PUBLISHED & COPYRIGHTED 1943 BY FRANK J. LOWE.

POLYCYCLINE *is the* ONLY *tetracycline produced directly by fermentation from a new species of Streptomyces isolated by Bristol Laboratories . . . rather than by the chemical modification of older antibiotics.*



The most modern
Broad-Spectrum Antibiotic

POLYCYCLINE

TRADE MARK

(TETRACYCLINE *Bristol*)

- the only tetracycline produced directly by fermentation from a new species of Streptomyces isolated by Bristol Laboratories...rather than by the chemical modification of older broad-spectrum antibiotics.
- ***effective in broad range***
  against gram-positive and gram-negative organisms.
- ***less toxic***
  (lower incidence of side reactions)
  than older broad-spectrum antibiotics.
- ***more soluble***
  than chlortetracycline (quicker absorption, wider diffusion).
- ***more stable in solution***
  than chlortetracycline or oxytetracycline
  (higher, more sustained, blood levels).

Now available as

POLYCYCLINE SUSPENSION 250

(TETRACYCLINE *Bristol*)

—the ONLY oral suspension of tetracycline that is **ready-to-use.** Requires no reconstitution, no addition of diluent, **no refrigeration**—stable at room temperature for 18 months. Has appealing "crushed-fruit" flavor. Supplied in bottles of 30 cc., in concentration of 250 mg. per 5 cc.

Also available as

POLYCYCLINE CAPSULES

(TETRACYCLINE *Bristol*)

— 100 mg., bottles of 25 and 100.
— 250 mg., bottles of 16 and 100.

Dosage:
average adult,
1 gram daily, divided doses;
children in proportion
to body weight.

Bristol
LABORATORIES INC.
SYRACUSE, NEW YORK

CLINICAL REPORT ON ANSOLYSEN . . . NEW ANTIHYPERTENSIVE AGENT

ANSOLYSEN—pentolinium tartrate—is a potent ganglionic blocking agent which presents the advantage of comparative freedom from by-effects. This effective hypotensive agent is recommended for use in patients with moderate to severe hypertension.

Comparing the effects of hexamethonium and ANSOLYSEN in 27 patients with severe "fixed" hypertension, Freis and coworkers[1] observed:

ANSOLYSEN was approximately five times more potent than hexamethonium

ANSOLYSEN produced less tolerance

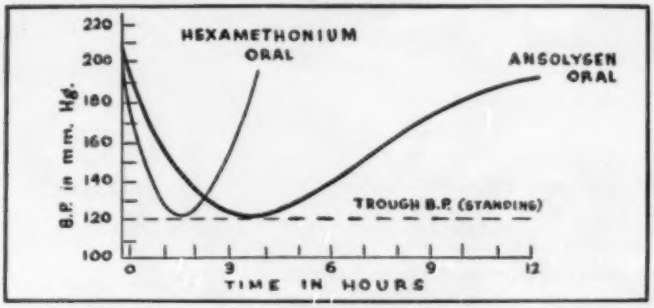
ANSOLYSEN's hypotensive effect was 40% longer

ANSOLYSEN's hypotensive effect was more predictable

ANSOLYSEN caused less pronounced by-effects

ANSOLYSEN caused less constipation

ANSOLYSEN lowered the blood pressure significantly, with little or no risk of producing collapse reactions or paralytic ileus



Changes in blood pressure noted by Smirk[2] after therapeutic oral doses of hexamethonium and ANSOLYSEN.

Supplied: Scored tablets—40 and 100 mg., bottles of 100
Injection—10 mg. per cc., vials of 10 cc.

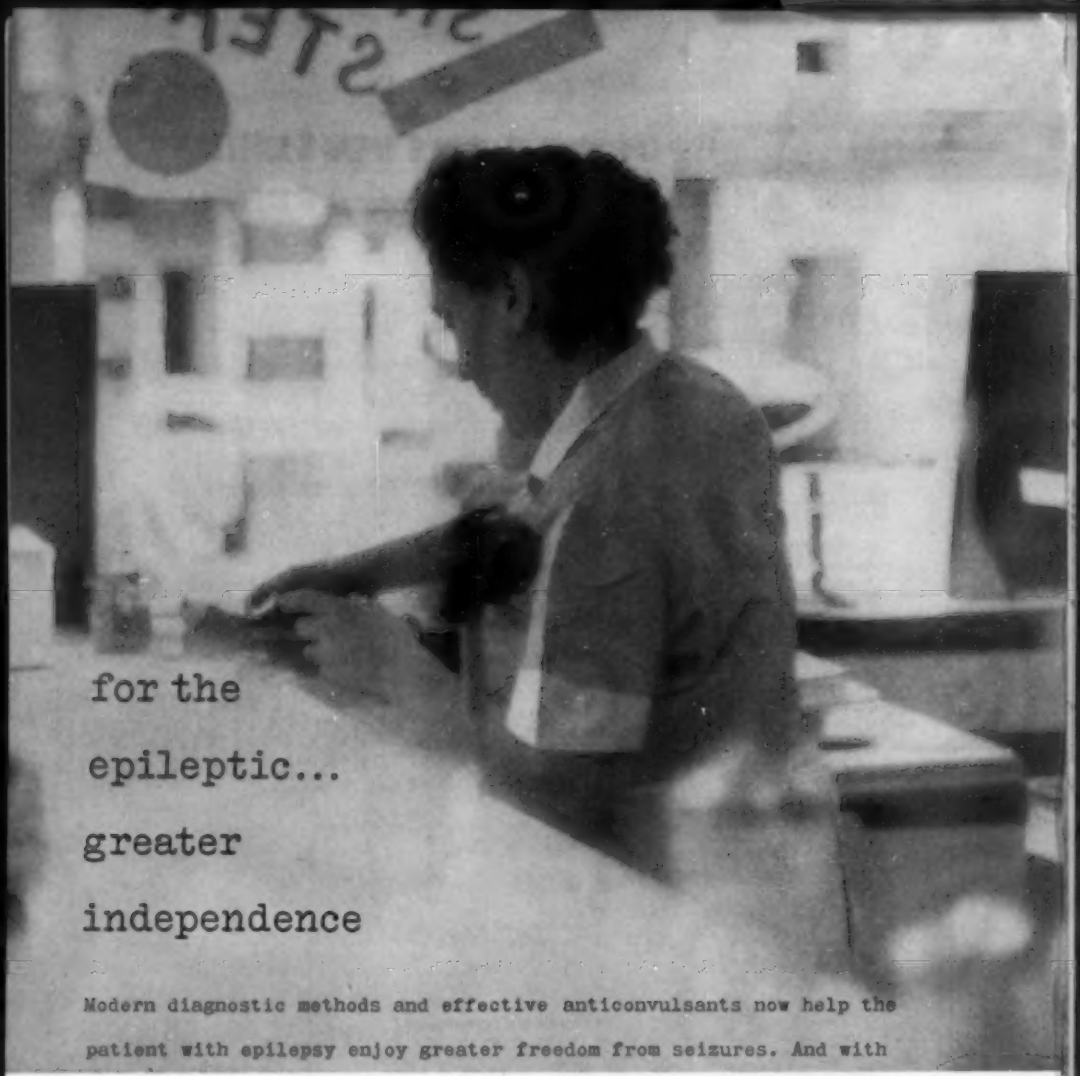
1. Freis, E. D., and others: Circulation 9:540 (April) 1954
2. Smirk, F.H.: New Zealand M.J. 52:1 (Oct.) 1953

ANSOLYSEN*

PENTOLINIUM TARTRATE

*Trademark

Wyeth
Philadelphia 2, Pa.



for the
epileptic...
greater
independence

Modern diagnostic methods and effective anticonvulsants now help the patient with epilepsy enjoy greater freedom from seizures. And with a more understanding society, greater independence is assured.

DILANTIN® SODIUM (diphenylhydantoin sodium, Parke-Davis)

an established anticonvulsant of choice, alone or in combination, for control of grand mal and psychomotor seizures -- without the handicap of somnolence.

DILANTIN Sodium is supplied in a variety of forms -- including Kapseals® of 0.03 Gm. (½ gr.) and 0.1 Gm. (1½ gr.) in bottles of 100 and 1,000.

Parke, Davis & Company

For every patient
with clearcut menopausal
symptoms such as **hot flushes,**
there's another patient with symptoms less clearly defined
yet just as distressing . . . headaches,
insomnia, mental and physical fatigue.
Her symptoms may also be indicative of declining ovarian function, and occur
several years before, and even long after, menstruation ceases.
This patient, too, may be expected to **benefit** from "Premarin" therapy.

"PREMARIN"® is a complete equine estrogen-complex.
It not only produces prompt symptomatic relief, but also imparts
a distinctive **"sense of well-being"**
highly gratifying to the patient. It is tasteless and odorless.
"Premarin," estrogenic substances (water-soluble),
also known as conjugated estrogens
(equine), is supplied in tablet
and liquid form.

Ayerst

New York, N. Y. • Montreal, Canada

NOW the safest agent yet developed for decisive control of BLOOD PRESSURE with 5 important firsts

UNITENSEN

brand of cryptenamine

Unitensen is recommended for the patient who needs more than tranquilizing effects. It produces positive, sustained falls in blood pressure.

This is what Unitensen Tablets do . . . and with unparalleled safety

Summary of Case Histories-Series A*

Age—Sex	BP—mm. Hg. BEFORE	BP—mm. Hg. AFTER
64—M	190/115	140/90
37—M	200/130	130/85
48—M	230/140	140/100
46—M	220/140	160/110
41—M	210/140	155/110
43—M	200/120	160/110
26—M	230/130	180/120
44—M	220/130	175/120
46—M	220/120	162/90

These patients experienced sustained control of blood pressure levels over prolonged periods of time.

(Write for complete clinical data, including case histories.)

*Personal communication to Irwin, Neisler & Company.

FIRST IN MAINTAINING DECISIVE BLOOD PRESSURE CONTROL

The sole therapeutic agent in Unitensen Tablets is cryptenamine—a potent blood pressure lowering alkaloid fraction isolated by the research staff of Irwin, Neisler & Company. In the majority of cases (see chart at left), cryptenamine will lower blood pressure decisively, and will control blood pressure at the lower levels for prolonged periods of time.

FIRST IN SAFETY

Unitensen Tablets exert a central action on the blood pressure lowering mechanism. Circulatory equilibrium is not disrupted. Improved circulation and improved work of the heart are often attained, *along with the decisive fall in blood pressure.*

Unitensen Tablets have no sympatholytic or parasympatholytic action. Ganglionic blocking does not occur. Unitensen Tablets *do not* cause postural hypotension and collapse, an ever-present risk with other potent blood pressure lowering drugs. Renal function is *not* impaired.

EN®

TANNATE TABLETS

Bottles of 50, 100, 500 and 1000.

FIRST WITH DUAL ASSAY

Unitensen is biologically standardized twice, first for hypotensive response and, second, for side effects (emesis) in the dog so that a safe therapeutic range between the two is assured. In extensive clinical trials only a few isolated cases exhibited occasional vomiting.

Unitensen Tablets do not cause the serious side effects common to widely used synthetic hypotensives. Unitensen Tablets can be given over long periods of time with entire dependability. Cumulative effects have not been noted.

FIRST IN SIMPLE DOSAGE

Start with 2 tablets daily, given immediately after breakfast and at bedtime. If more tablets are needed, include an afternoon dose at 1 or 2 p.m.

FIRST IN ECONOMY

Because of lower dosage, Unitensen Tablets save your patients ⅓ to ½ over the cost of other potent blood pressure lowering agents.

Each Unitensen Tablet contains: Cryptenamine*..... 2 mg.†
(as the tannate salt)

*Ester alkaloids of Veratrum viride obtained by an exclusive Irwin-Neisler nonaqueous extraction process. †Equivalent to 260 Carotid Sinus Reflex Units.

IRWIN, NEISLER & COMPANY DECATUR, ILLINOIS

four good things happen to your peptic ulcer patient when Kolantyl goes to work

Painful gastrointestinal spasm is relieved · hyperacidity is neutralized · cellular repair is encouraged · mechanical erosion is arrested (1). Give your next ulcer patient economical 4-way relief. Prescribe pleasant-tasting KOLANTYL GEL.

(1) Johnston, R. L.: J. Ind. St. Med. Assn. 46:869, 1953
(2) McHardy, G. and Browne, D.: Soc. Med. J. 45:1139, 1952

Merrell
Since 1828

Kolantyl Gel

Rx INFORMATION

Action:

1. Bentyl* combines spasmolysis and parasympathetic-depressant actions without the side effects of atropine.
2. Prompt, prolonged neutralization of excess gastric acidity... magnesium oxide and aluminum hydroxide.
3. Protective, demulcent coating action over the ulcerated area ... methylcellulose.
4. Checks the mucus-destroying action of lysozyme and pepsin... sodium lauryl sulfate.

*Merrell's distinctive antispasmodic that is more effective than atropine —free from side effects of atropine.[2]

Composition: Each 10 cc. of Kolantyl Gel or each Kolantyl tablet contains:

Bentyl Hydrochloride . .	5 mg.
Aluminum Hydroxide Gel	400 mg.
Magnesium Oxide	200 mg.
Sodium Lauryl Sulfate .	25 mg.
Methylcellulose	100 mg.

Dosage: Gel—2 to 4 teaspoonfuls every three hours, or as needed. Tablets—2 tablets (chewed for more rapid action) every three hours, or as needed.

Supplied: Gel—12 oz. bottles. Tablets—bottles of 100 and 1,000.

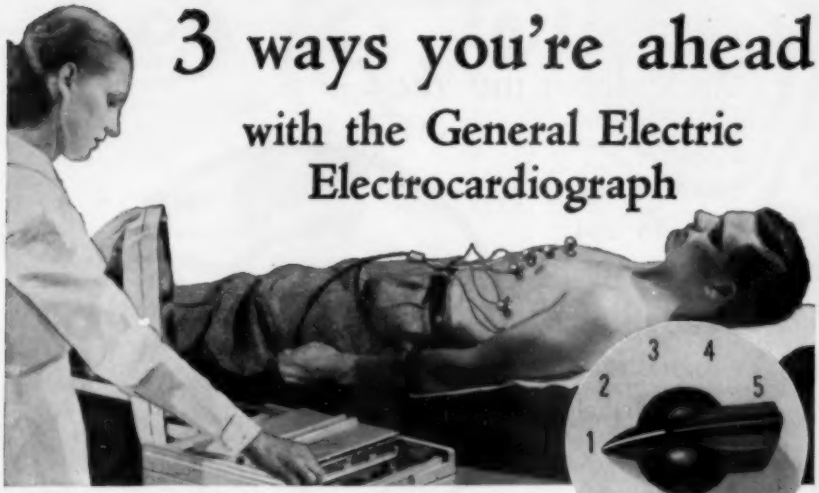
T. M. Kolantyl®, 'Bentyl'.

The Wm. S. Merrell Company
CINCINNATI
New York • St. Thomas, Ontario

PIONEER IN MEDICINE FOR OVER 125 YEARS

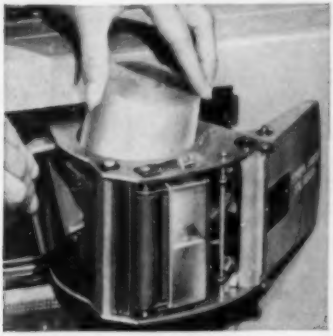
3 ways you're ahead

with the General Electric Electrocardiograph



1 Exclusive switch selection for simpler, faster recordings

Without changing electrodes, you can take up to *30 leads*, including six chest positions. Once the patient electrodes are in place, you can take leads 1, 2, 3, aVR, aVL, aVF, and the 1 to 6 positions at V, CR, CL and CF by merely turning selector switches.



2 New paper drive for easier loading, greater accuracy

Using a new type of roller and a synchronous motor, General Electric assures uniform paper speed for accurate measurement of conduction times. Loading is simple — nothing to disassemble. Just flip open hinged door . . . place paper roll on spindle . . . thread through simple guides . . . and snap unit back in place. *All in a few seconds.*

3 New cabinet design for easier operation and carrying, added safety

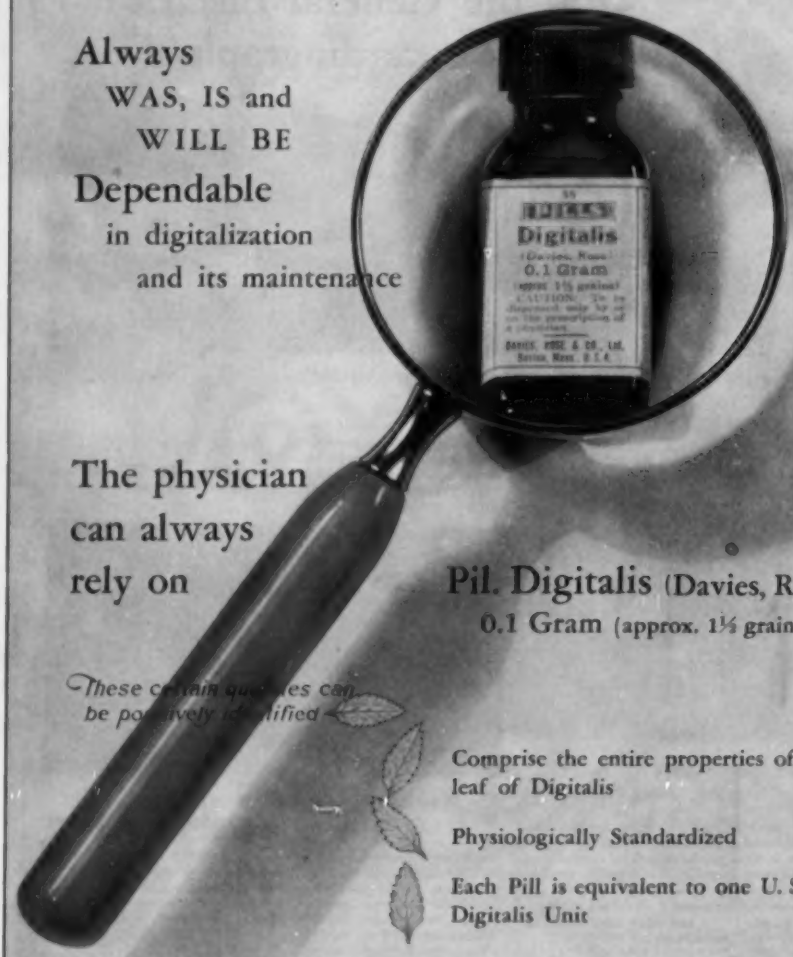
Dual hinged covers open at a touch, making recessed controls immediately accessible. Cover supports no weight when unit is carried — handle attaches to main case. For all the facts on the DWB Cardioscribe, see your G-E x-ray representative. Or write X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. M-115.

Progress Is Our Most Important Product

GENERAL ELECTRIC

Made from the *leaf*—

Always
WAS, IS and
WILL BE
Dependable
in digitalization
and its maintenance



The physician
can always
rely on

Pil. Digitalis (Davies, Rose)
0.1 Gram (approx. 1½ grains)

These certain qualities can be positively identified

Comprise the entire properties of the leaf of Digitalis

Physiologically Standardized

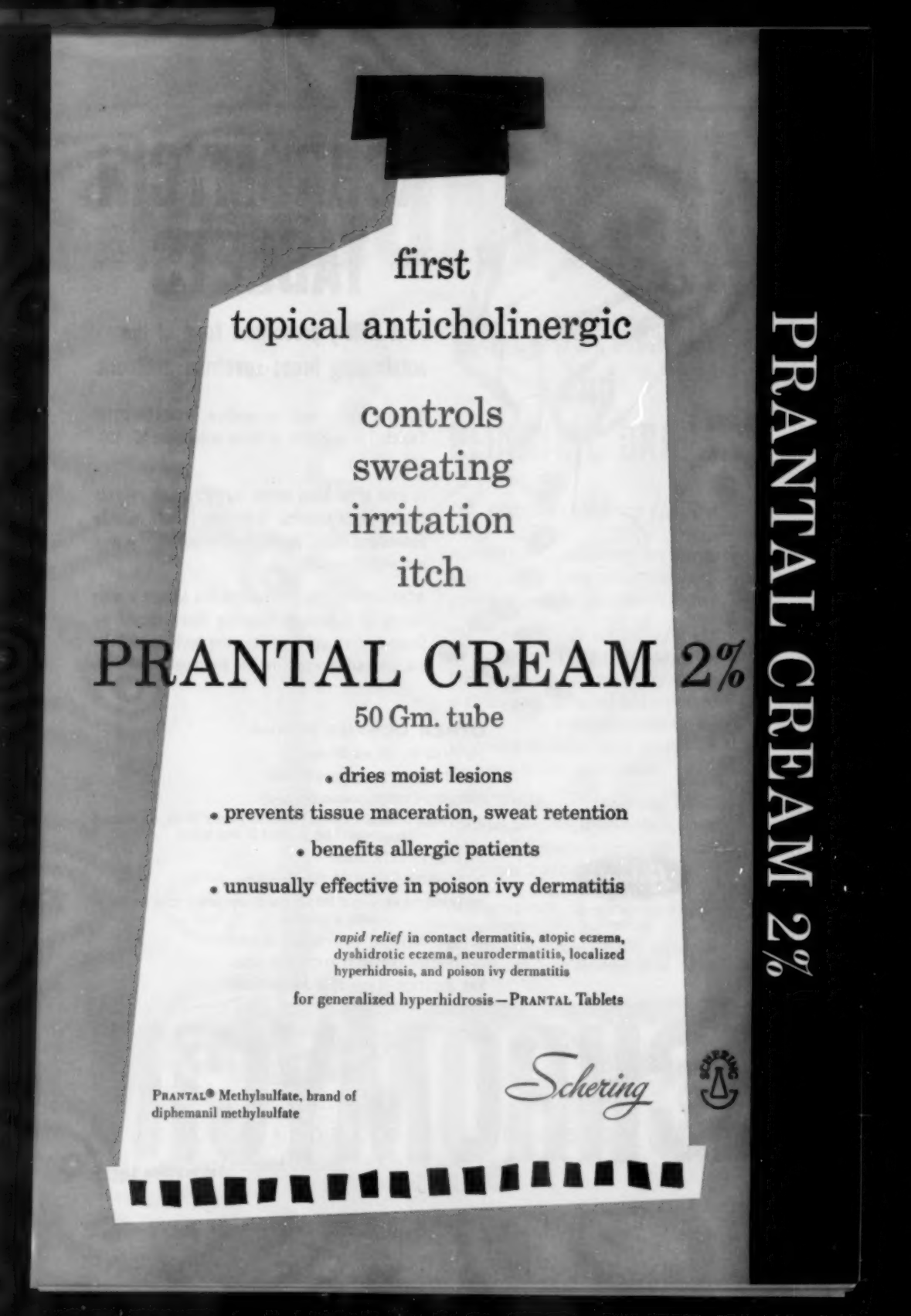
Each Pill is equivalent to one U. S. P. Digitalis Unit

Clinical samples and literature sent to physicians on request

Davies, Rose & Company, Limited Boston 18, Mass.

PHARMACEUTICAL MANUFACTURERS

D23


first
topical anticholinergic
controls
sweating
irritation
itch
PRANTAL CREAM 2%
50 Gm. tube
• dries moist lesions
• prevents tissue maceration, sweat retention
• benefits allergic patients
• unusually effective in poison ivy dermatitis
rapid relief in contact dermatitis, atopic eczema, dyshidrotic eczema, neurodermatitis, localized hyperhidrosis, and poison ivy dermatitis
for generalized hyperhidrosis—PRANTAL Tablets
PRANTAL® Methylsulfate, brand of diphemanil methylsulfate
Schering
PRANTAL CREAM 2%

ACHROMYCIN
TETRACYCLINE
TABLETS

A widely prescribed form of the outstanding broad-spectrum antibiotic

Sugar-coated, easy-to-swallow ACHROMYCIN Tablets are available in three potencies: 50, 100, and 250 mg.

In each of its many forms, ACHROMYCIN exhibits notable characteristics: it diffuses rapidly in body tissues and fluids; gastrointestinal irritation is rare and mild in nature.

ACHROMYCIN has proved effective against a wide variety of infections including those caused by Gram-positive and Gram-negative bacteria, rickettsia, and certain virus-like and protozoan organisms.

OTHER DOSAGE FORMS

CAPSULES: 50, 100, and 250 mg.

PEDIATRIC DROPS: (see opposite page)

ORAL SUSPENSION: (see opposite page)

SPERSOIDS® Dispersible Powder (Chocolate Flavor): 50 mg. per rounded teaspoonful (3 Gm.), 12 and 25 dose bottles

SOLUBLE TABLETS: 50 mg.

INTRAVENOUS: vials of 100, 250, and 500 mg.

INTRAMUSCULAR: vials of 100 mg. (for dilution with 2 cc. of sterile water or saline)

TOPICAL OINTMENT (3%): ½ and 1 oz. tubes

OPHTHALMIC OINTMENT (1%): ⅛ oz. tubes

EAR SOLUTION (0.5%): 10 cc. dropper bottles

Lederle

®REG. U.S. PAT. OFF.

ACHROMYCIN*

Tetracycline Lederle

ACHROMYCIN*

Tetracycline Lederle

ORAL SUSPENSION and PEDIATRIC DROPS

popular cherry flavor

ACHROMYCIN is available in two cherry-flavored dosage forms that are highly acceptable to patients—particularly children.

The Pediatric Drops are packaged with an easy-to-read graduated dropper. The Oral Suspension, supplied as dry crystals in a 1 oz. bottle. Both Oral Suspension and Pediatric Drops, when reconstituted by the pharmacist or nurse, retain potency for two weeks at room temperature.

ACHROMYCIN, an outstanding broad-spectrum antibiotic, is relatively free from untoward side reactions and provides rapid diffusion in body tissues and fluids.

ORAL SUSPENSION (Cherry Flavor): 250 mg. per teaspoonful (5 cc.), 1 oz. bottles

PEDIATRIC DROPS (Cherry Flavor): 100 mg. per cc. (approx. 5 mg. per drop), 10 cc. bottles

*REG. U.S. PAT. OFF.

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY PEARL RIVER, N.Y.

Lederle

Viso-Cardiette Interpretation

Only an *accurate* electrocardiogram will provide the physician or cardiologist with the true information that he seeks. And from the abnormalities of a 'cardiogram the abnormalities of the corresponding portions of the heart can be read. Likewise Viso records present a 'cardiographic pattern which mirrors the true worth of the instrument.

Performance of the Viso means the extremely simplified manner in which records are obtained. Routine testing time, patient connection included, averages about seven minutes.

Quality of appearance of the Viso is an outward indication of a quality within. And its inward quality of construction conduces to the Sanborn *quality of results.*

Reliability of the Viso is practically assured by the Sanborn background of over *thirty years* of ECG design and manufacture. Simply ask any Viso owner about Viso!

Service by Sanborn is something to be sure of. A network of offices includes *thirty* in centrally located cities throughout the country, and exclusive Service Helps by mail are available to *every* owner.

Trial Plan the Viso way means your privilege to test a machine *in your* practice for 15 days *without any obligation whatsoever.* Write for details and descriptive literature.

SANBORN COMPANY
195 Massachusetts Avenue, Cambridge 39, Massachusetts

full therapeutic effects of aminophylline - ORALLY

for:

BRONCHIAL AND CARDIAC ASTHMA

CONGESTIVE HEART FAILURE

PAROXYSMAL DYSPNEA

EDEMATOUS STATES

AMINODROX-FORTE supplies aminophylline, combined with a specially prepared aluminum hydroxide which minimizes gastric irritation, yet permits rapid absorption. Daily ORAL dosage can be tolerated to produce and maintain the constant, high blood levels necessary for effective therapy.

AMINODROX-FORTE, containing 3 gr. of Aminophylline, permits dosage flexibility. Smaller, frequently repeated doses provide sustained therapeutic blood levels and further diminish the incidence of undesirable side reactions.

AMINODROX® - FORTE

each Aminodrox-Forte tablet contains:

Aminophylline ..... 3 gr.

Aluminum Hydroxide Gel, dried ..... 4 gr.

send for professional literature and samples

THE S. E. MASSENGILL COMPANY
BRISTOL, TENNESSEE

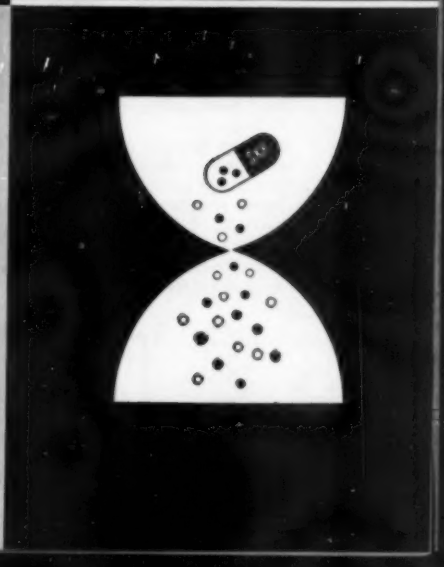
. . . a "confused" old lady

'Dexamyl' helped

. . . an extremely nervous man

(Photographs and excerpts of case histories from the files of a general practitioner.)

Remember: 'Dexamyl' is now available in the unique 'Spansule' capsule dosage form—to provide smooth, prolonged, uninterrupted mood-ameliorating effect for a period of 10-12 hours—*with just one oral dose.* 'Dexamyl' *Spansule* capsules are available in two strengths (see lower right, facing page).



Patient S. M. (80) was "plagued with nervousness, profound weakness, vertigo, and pain . . . add to this the untimely catastrophic death of a daughter."

'Dexamyl' relieved "her nervous uncertainty, her depressive weariness, her melancholia, and her tearfulness . . . also her vertigo . . . 'Dexamyl' helped her to smile again."

Patient L. H. (51) "had positive tremors of the eyelids, tongue, fingers, lips and voice . . . His complaints always centered about extreme nervousness, jitteriness, depression, and 'all-gone weakness'.

" 'Dexamyl' allayed inward tension . . . gave him a sensation of amelioration and comfort . . . Yet, even in this intensely irritable patient, there were no side effects . . .

"He is now able to work and support himself, which he was unable to do for several years."

Dexamyl*

tablets—elixir—Spansule† capsules

relieves both anxiety

and depression—promotes

a feeling of composure

'Dexamyl' provides the synergistic action of two mood-ameliorating components: 'Dexedrine' and amobarbital.

Tablets—each containing Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital, ½ gr. (32 mg.).

Elixir—each teaspoonful (5 cc.) equivalent to one Tablet.

'Dexamyl' ***Spansule*** **(No. 1)**—each containing the equivalent of *two* tablets: 'Dexedrine' Sulfate, 10 mg.; amobarbital, 1 gr. (65 mg.).

'Dexamyl' ***Spansule*** **(No. 2)**—each containing the equivalent of *three* tablets: 'Dexedrine' Sulfate, 15 mg.; amobarbital, 1½ gr. (97 mg.).

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of sustained release capsules (patent applied for).

"A program of treatment for *chronic ulcerative colitis...*

as described by Lester M. Morrison, M.D., Los Angeles[1]

...is based on the use of 1) azopyrine*, 2) ACTH or cortisone and 3) psychotherapy."

"Azopyrine* ... has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."

1. Rev. Gastroenterology 20:744 (Oct.) 1953; abstract in J. A. M. A., 153:1580 (Dec. 26) 1953.

*now available under the name ...

Azulfidine®

BRAND OF SALICYLAZOSULFAPYRIDINE

Reports on Azulfidine:

(This drug has been presented under three different names, which appear in the literature cited, viz: Salazopyrin, Azopyrin and the now established name in America, Azulfidine.)

1949 "The administration of salicylazosulfapyridine (salazopyrin) produced marked improvement in 8 of 12 cases of ulcerative colitis."

Bargen, J. A.: Med. Clin. North America, 33:935 (July) 1949.

1950 Bargen reports that since 1949 approximately 100 patients have been treated with Azulfidine. "The results have been extremely satisfactory in most cases."

Personal communication (Apr. 12)

1951 After-control data 1949 from 119 patients treated with Azulfidine prior to 1944 showed 90 patients (84%) symptom-free or considerably improved.

Svartz, N.: Acta Med. Scandinav. 141:172, 1951.

1952 In a series of 52 patients with chronic ulcerative colitis 30 or 58% showed significant improvement after treatment with Azulfidine.

Morrison, L. M.: Gastroenterology 21:133, 1952.

1953 Morrison publishes results from a series of 47 patients treated with Azulfidine compared to a control series of 60 patients receiving other current therapy: In the Azulfidine-series 18% are symptom-free and 52% improved, compared to 5% and 32% respectively, in the control series.

J. A. M. A.: 151:366 (Jan. 31) 1953.

literature on request from

PHARMACIA LABORATORIES, Inc.

Executive Offices: 270 Park Ave., New York 17, N. Y., Sales Offices: 300 First St., N.E. Rochester, Minn.

These are the Gantrisin advantages —

Gantrisin 'Roche' is a single, soluble, wide-spectrum sulfonamide -- especially soluble at the pH of the kidneys. That's why it is so well tolerated...does not cause renal blocking...does not require alkalies. Produces high plasma as well as high urine levels. Over 250 references to Gantrisin® in recent literature.

—and these are the reasons for Gantricillin

It provides Gantrisin PLUS penicillin...for well-tolerated, wide-spectrum antibacterial therapy...in tablets of two strengths -- Gantricillin®-300 for severe cases; Gantricillin (100) for mild cases -- and in an easy-to-take suspension for children -- Gantricillin (acetyl)-200

'Roche.'

IN TENSION AND HYPERTENSION

sedation without hypnosis

℞ Serpasil T.M.

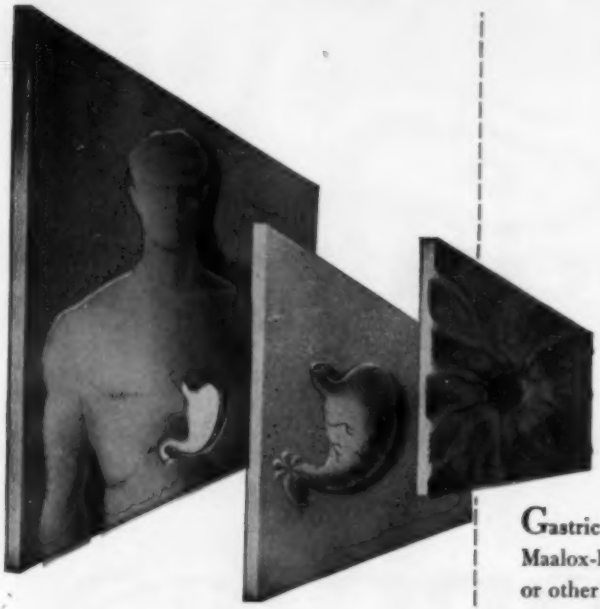
(reserpine CIBA)

A pure crystalline alkaloid of rauwolfia root first identified, purified and introduced by CIBA

In anxiety, tension, nervousness and mild to severe neuroses—**as well as in hypertension**—SERPASIL provides a nonsoporific tranquilizing effect and a sense of well-being. Tablets, 0.25 mg. (scored) and 0.1 mg.

CIBA

SUMMIT, N. J.



maalox®

gives ulcer relief

without side effects

Gastric hyperacidity is controlled by Maalox-Rorer without constipation [9] or other side effects commonly encountered with antacids. Relief of pain and epigastric distress is prompt and long-lasting. Available in tablets and liquid form.

Suspension Maalox-Rorer contains the hydroxides of Magnesium and Aluminum in colloidal form. The smooth texture and pleasant flavor make it highly acceptable, even with prolonged use.

Supplied: in 355 cc. (12 fluid ounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension Maalox.)

Samples will be sent promptly on request.

WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square

Philadelphia 6, Pa.

Clinicopharmacologic Properties of Gitaligin®

[Brand of Amorphous Gitalin]

The following table is quoted verbatim from the report by Dimitroff, S.P.; Griffith, G.C.; Thorner, M.C. and Walker, J.: Clinical Evaluation of Gitalin in the Treatment of Congestive Heart Failure, Annals Int. M. 39:1189 (Dec.) 1953.

Derivation	*Digitalis purpurea.*
Appearance	Amorphous white powder.
Uniformity	Constant from batch to batch.
Absorption	Rapid and complete from gastrointestinal tract.
Route of administration	Oral.
Dissipation	Rate of excretion between the rapidly excreted Digoxin and slowly excreted leaf or digitoxin.
Range of toxicity	Less toxic than other glycosides. Digitalizing dose is about 1/3 amount of the toxic dose.
Dosage by rapid method	2.5 mg. first, then 1.0 mg. every 6 hours, or 1.0 mg. every 4-6 hours until toxic or therapeutic effect appears (usually 24-48 hours.)
Dosage by slow method	A single dose of 1.5 mg. daily, or 0.5 mg. t.i.d. until toxic or therapeutic effect appears (usualy 4-7 days).
Symptoms of toxicity	Same as for other glycosides, i.e., anorexia, nausea, vomiting, color-vision, ectopic beats, ST-T changes.

WHITE LABORATORIES, INC., Kenilworth, N.J.

Simple dosage equivalent: 0.5 mg. (1 tablet) of Gitaligin is approximately equivalent to 0.1 Gm. (1½ gr.) digitalis leaf. Gitaligin is supplied in 0.5 mg. tablets, deep scored for accuracy and flexibility of dosage—in bottles of 30 and 100.

Gitaligin is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

compare before you prescribe

modern criteria of good digitalis therapy

1. pure active principle
2. complete absorption
3. rapid onset of action
4. smooth, even maintenance
5. frequent dosage readjustment unnecessary
6. virtual freedom from gastric upset

digitaline nativelle®

conforms to the rigid criteria of a modern cardiotonic and provides oral, I.M., and I.V. forms for flexibility of dosage

compare *then prescribe...*

DIGITALINE NATIVELLE

—the original pure crystalline digitoxin

Consult your Physicians' Desk Reference for dosage information.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

quick . . . . . what's a good B complex?

SUR-BEX®

(Abbott's Vitamin B Complex Tablets)

or SUR-BEX with Vitamin C

(Contains 150 mg. of ascorbic acid in addition to the B complex factors below)

just 1 SUR-BEX tablet a day supplies:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
Liver Fraction 2, N.F.	300 mg.
Brewer's Yeast, Dried	150 mg.

Abbott

408177

CONVERTIN supports digestive function by selective release of:

hydrochloric acid in the stomach, and desoxycholic acid and pancreatin in the small intestine.

Experience shows that the supplementation of gastric and pancreatic digestants is normally beneficial among the elderly.[1-3]

CONVERTIN®

digestant tablets

permit a more varied diet . . . better nutrition . . . by partial replacement of digestants diminished with age.

Each CONVERTIN Tablet is actually two tablets in one:

A sugar-coated outer layer designed to release in the stomach:

Betaine HCl . . . 130.0 mg. *(Provides 5 minims Diluted Hydrochloric Acid U.S.P.)* ***and***
Oleoresin Ginger . . . 1/600 gr.

Surrounding an enteric-coated core designed to release in the small intestine:

Pancreatin . . . 62.5 mg. *(Equiv. to 250 mg. U.S.P.)* ***and***
Desoxycholic Acid . . . 50.0 mg.

DOSAGE: Two tablets with or just after meals. Dose may be reduced, usually after first week, at the discretion of the physician.

SUPPLIED: In bottles of 84 and 500 tablets.

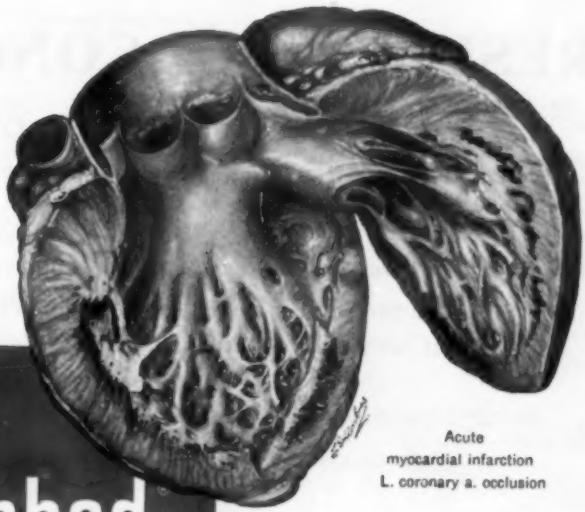
Available on prescription only

B.F. ASCHER & COMPANY, INC.
Ethical Medicinals
KANSAS CITY, MO.

References: 1. Lee, R. I.: Chicago M. Soc. Bull.: 48:503, 1946. 2. Golob, M.: Am. J. Digest. Dis. 18:308, 1951. 3. McLester, J. S., and Darby, W. J.: Nutrition and Diet in Health and Disease, ed. 6, Philadelphia, W. B. Saunders Company, 1952, pp. 416, 476.

—in the severe shock

secondary to myocardial infarction



Acute
myocardial infarction
L. coronary a. occlusion

WINTHROP

Levophed

BITARTRATE

..... may be life-saving

A series of 14 cases of severe shock accompanying myocardial infarction was treated by various methods. All of the 6 patients who received Levophed recovered despite the presence of congestive heart failure.[1]

The practically instant pressor effect of Levophed—within 10 to 30 seconds—may usually be maintained at desired levels almost indefinitely.

Write for detailed literature.

Winthrop-Stearns INC.
NEW YORK 18, N. Y. • WINDSOR, ONT.

1. Gazes, P. C., Goldberg, L. I., and Darby, T. D.: *Circulation*, 8: 883, Dec., 1953.

Levophed bitartrate, brand of levarterenol bitartrate

RONCOVITE (Cobalt-Iron) has introduced a wholly new concept in anti-anemia therapy. It is based upon the unique hemopoietic stimulation produced only by cobalt. The application of this new concept has led to marked, often dramatic, advances in the successful treatment of many of the anemias.

RESULTS ARE CONCLUSIVE

The Wide Acceptance of Cobalt-Iron Therapy Stems from Findings Like These:*

High Percentage of Patient Response--

Of 42 pregnant patients, 41 maintained or improved their hemoglobin status.[1]

Better Hemoglobin Synthesis--

Cobalt accelerates utilization of iron in hemoglobin synthesis.[2]

Greater Erythropoiesis--

"...increased erythropoietic activity would preclude the need for transfusion."[3]

Rapid Improvement--

Response more rapid than intravenous iron.[4]

Optimum Results--

Cobalt should be given with iron to produce optimum results.[5]

Clinical Safety--

Even in prematures, no harmful effects were noted despite high dosage.[6]

SUPPLIED

RONCOVITE TABLETS

Each enteric coated, red tablet contains:

Cobalt chloride.....15 mg.
Ferrous sulfate exsiccated.....0.2 Gm.

RONCOVITE DROPS

Each 0.6 cc. (10 drops) provides:

Cobalt chloride.....40 mg.
(Cobalt.....9.9 mg.)
Ferrous sulfate.....75 mg.

RONCOVITE-OB

Each enteric coated, red capsule-shaped tablet contains:

Cobalt chloride.....15 mg.
Ferrous sulfate exsiccated.....0.2 Gm.
Calcium lactate.....0.9 Gm.
Vitamin D.....250 units

DOSAGE

One tablet after each meal and at bedtime; 0.6 cc. (10 drops) in water, milk, fruit or vegetable juice once daily for infants and children.

RONCOVITE

The original, clinically proved, cobalt-iron product.

*Bibliography of 192 references available on request.

1. Holly, R.G.: The Value of Iron Therapy in Pregnancy, Journal-Lancet 74:211 (June) 1954.
2. Kato, K.: Iron Cobalt Treatment of Physiologic and Nutritional Anemia in Infants, J. Pediat., 11:385 (Sept.) 1937.
3. Gardner, F.: The Use of Cobaltous Chloride in the Anemia Associated with Chronic Renal Disease, J. Lab. & Clin. Med., 41:56 (Jan.) 1953.
4. Weissbecker, L.: Cobalt Therapy, Dtsch. M. Wschr., 75:116 (1950).
5. Coles, B.L., and James, U.: The Effect of Cobalt and Iron Salts on the Anaemia of Prematurity, Arch. Disease in Childhood 29:85 (1954).
6. Quilligan, J.J., Jr.: Effect of a Cobalt-Iron Mixture on the Anemia of Prematurity, Texas St. J. Med. 50:294 (May) 1954.

LLOYD BROTHERS, INC.

Cincinnati 3, Ohio

potent hematinic...

Fully adequate for the oral treatment of pernicious anemia and other macrocytic anemias. Meets U.S.P. specifications.

Contains **extra** amounts of B_{12}

Patterned after Spies' basic formula,* provides a full complement of other essential or accessory hemopoietic factors for optimum response in the treatment of the common anemias.

Recommended daily dosage (3 capsules) contains:

Vitamin B_{12} with intrinsic factor concentrate .....1 U.S.P. Unit

Vitamin B_{12} U.S.P. (crystalline) .....75.0 mcg.

Folic acid U.S.P..... 5.0 mg.
Vitamin C (ascorbic acid)..150.0 mg.
Thiamine mononitrate (B_1). 10.0 mg.
Riboflavin (B_2) ..... 10.0 mg.
Nicotinamide .....150.0 mg.
Ferrous sulfate exsic.....600.0 mg.

"CLUSINTRIN"

for effective, practical antianemia therapy

Indications: Treatment of pernicious anemia and other macrocytic hyperchromic anemias; microcytic hypochromic anemia.
Availability: No. 316 — Supplied in bottles of 100 and 1,000.
*Spies, T. D.: J.A.M.A. 145:66 (Jan. 13) 1951.

Ayerst **Ayerst Laboratories, New York, N. Y. • Montreal, Canada**

5450

for sedation

tranquilization without hypnosis

RAU-SED

SQUIBB RESERPINE

the chief sedative alkaloid
of rauwolfia

0.1 and 0.25 mg. tablets,
bottles of 100 and 1,000.
0.5 mg. tablets,
bottles of 50 and 500.

---

in hypertension

RAUDIXIN

SQUIBB RAUWOLFIA

contains *all* the alkaloids
of rauwolfia

50 and 100 mg. tablets,
bottles of 100 and 1,000.

SQUIBB

"RAU-SED" AND "RAUDIXIN" ® ARE SQUIBB TRADEMARKS

24-hour control

for the majority of diabetics

GLOBIN INSULIN

'B.W. & CO.'®

a clear solution . . . easy to measure accurately

Discovered by Reiner, Searle, and Lang
in The Wellcome Research Laboratories

BURROUGHS WELLCOME & CO. (U.S.A.) INC. • Tuckahoe 7, New York

Please Mention this Journal when writing to Advertisers

for new, safe,
nausea-free,
vomiting-free
comfort
in pregnancy

prescribe **Bonadoxin***
BRAND OF MECLIZINE HCl, PYRIDOXINE HCl
tablets

New combination attacks nausea and vomiting of pregnancy on two planes:

The Symptomatic Plane—Bonadoxin contains meclizine—the safe, longer-acting antiemetic with highly specific vestibular effects.

The Metabolic Plane—Bonadoxin contains pyridoxine—the enzyme-essential vitamin for which requirements are markedly increased during the first trimester. Its presence in high dosage helps restore proper carbohydrate metabolism, glycogen storage and hepatic function, thus correcting physiological derangements associated with "morning sickness."

Clinical results[1]: Abolished vomiting in 40 of 41 gravid women, eliminated nausea in 30 of 41. Less than 3% side effects. **Dosage:** 1 or 2 tablets, at bedtime. Larger doses if necessary. **Supplied:** Bottles of 25, prescription only. Each Bonadoxin Tablet contains 25 mg. meclizine hydrochloride, 50 mg. pyridoxine hydrochloride.

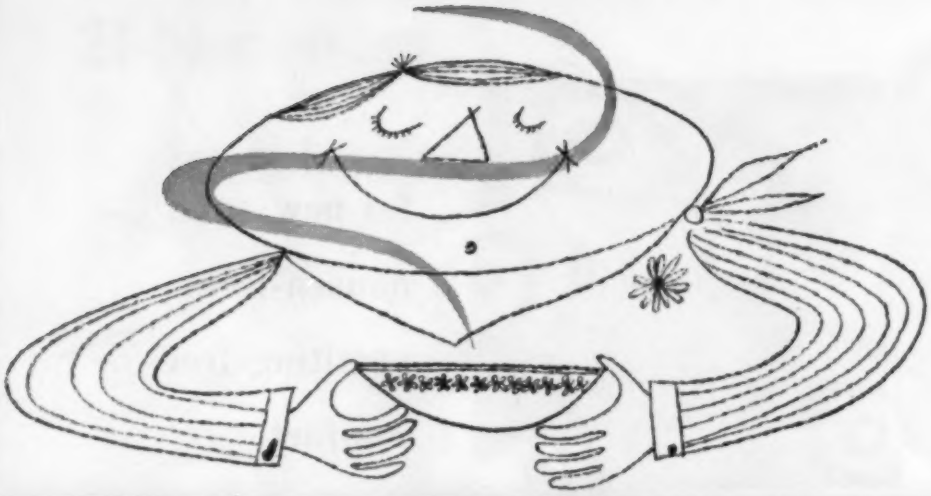
1. Garrett, T. A.: Personal communication.

*TRADEMARK

ROERIG Rx

Ethical Pharmaceuticals for Needs Basic to Medicine
536 Lake Shore Drive, Chicago 11, Illinois

Mrs. Ox needs a nutritional buildup! Prescribe OBRON*—calcium, iron, plus 8 vitamins, 5 other



salt-free needn't mean flavor-free

DIASAL is enthusiastically endorsed by low-salt dieters for the zest and flavor it gives to pallid, sodium-restricted meals. So closely does it match the appearance, texture and taste of table salt that patient adherence to your diet instructions is virtually assured.

DIASAL contains only potassium chloride, glutamic acid and inert ingredients... no sodium, lithium, or ammonium. It may be used safely for extended periods, both at the table and in cooking. Because of its potassium, DIASAL may be a valuable prophylactic against potassium depletion.

DIASAL®

packaging: available in 2-ounce shakers and 8-ounce bottles. Send for liberal supplies of tasting samples and low-sodium-diet sheets for your patients.

FOUGERA

E. FOUGERA & COMPANY, INC.
75 Varick Street, New York 13, N. Y.

needed extra protein the patient will enjoy

Protenum—the pleasant-tasting protein diet supplement—is a pleasure to prescribe because patients find that it is a pleasure to take.

Delicious Protenum, with its chocolate flavor, is highly acceptable to patients of all ages, with meals or between meals. The finicky child, the convalescent, the pregnant woman, the geriatric patient—all welcome Protenum. Patients on therapeutic diets find that Protenum is an exceptionally easy way to ingest extra protein.

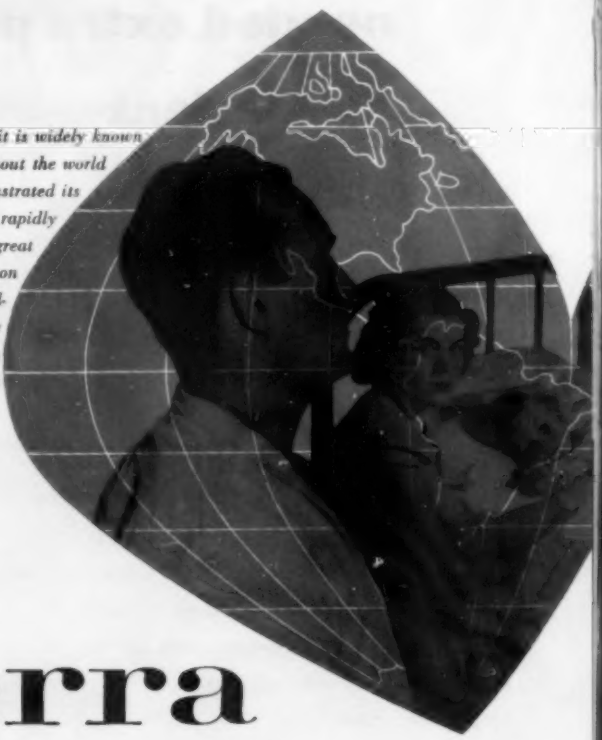
One glass of Protenum beverage (2 oz. Protenum powder and 5 oz. water) provides 24 Gm. of protein—as much as is contained in 4 eggs, or 4 oz. of sirloin steak, or 3 glasses of milk.

PROTENUM

The pleasant-tasting protein diet supplement

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A.

Because it is widely known throughout the world and has demonstrated its effectiveness in rapidly controlling the great majority of common infections, this broad-spectrum antibiotic is prescribed with certainty by physicians the world over.



terra cognita Terra

Supplied in the many convenient forms required in the practice of modern medicine: Capsules, Tablets (sugar coated), Pediatric Drops, Oral Suspension, Intravenous, Intramuscular, Ophthalmic (for solution), Ophthalmic Ointment, Ointment (topical), Vaginal Tablets, Troches, Otic, Nasal, Aerosol, Soluble Tablets and Topical Powder.

PROVED

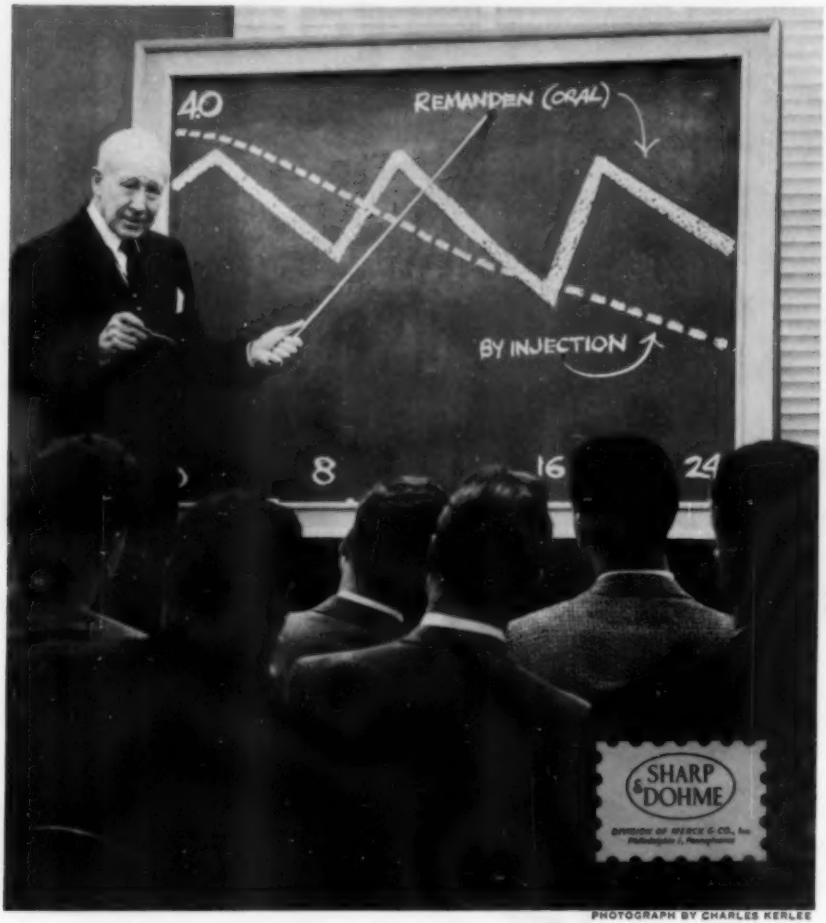
mycin®

BRAND OF OXYTETRACYCLINE

rapid absorption
wide distribution
prompt response
excellent toleration

Pfizer

PFIZER LABORATORIES, *Brooklyn 6, N.Y.*
DIVISION, CHAS. PFIZER & CO., INC.



PHOTOGRAPH BY CHARLES KERLEE

Note the sustained penicillin levels with oral

REMANDEN®

PENICILLIN WITH PROBENECID

REMANDEN produces the same high sustained plasma levels as intramuscular penicillin.[1] Because of the Benemid® (probenecid) content penicillin wastage is minimized. REMANDEN provides adequate oral penicillin therapy and also enhances the therapeutic effect of intramuscular procaine penicillin in the treatment of fulminating infections.

Reference: 1. Special Exhibit, Mod. Med. 22:94 (Jan.1) 1954.

Quick Information: REMANDEN-100 and REMANDEN-250 supply 0.25 *Gm.* 'Benemid' per tablet and 100,000 or 250,000 units of crystalline penicillin G. *Dosage: Adults:* 4 REMANDEN tablets initially, then 2 every 6 or 8 hours. *Children:* on basis of body weight. (Initial dose—25 mg. 'Benemid' per Kg.; daily dose—40 mg. per Kg. in divided doses every six hours.)

ANNALS OF
INTERNAL MEDICINE

VOLUME 41 NOVEMBER, 1954 NUMBER 5

ENDEMIC GOITER: A PROBLEM IN PREVENTIVE MEDICINE *

By DAVID MARINE, M.D., F.A.C.P., *Rehoboth, Delaware*

I wish to express to the Board of Regents my appreciation of the honor they have conferred upon me as their selection for the 1954 James D. Bruce Memorial Lecture in preventive medicine.

Dr. Bruce spent his entire medical career in an important endemic goiter region which I had occasion to visit several times, yet our paths never crossed.

My first visit to Michigan was in March, 1907, when I made a horse-and-buggy visit to several farms between Ann Arbor and Pontiac to get a first-hand acquaintance with endemic goiter in sheep and to add to our collection of thyroids of cretin and goitrous dogs and calves the thyroids of cretin lambs which were at that time not easily obtained in northern Ohio. More than 90 per cent of all dogs brought to the laboratory had hyperplastic thyroids.

Our collection, however, was not limited to field and abattoir sources. Some usable, though autolyzed, parenchymatous goiters of calves sold as sweetbreads were obtained in market stalls. It might be added that their very low iodine content would have made them non-injurious substitutes for true sweetbreads.

The results of the excursions into Michigan quickly tied in with my first visit to Chicago on May 23, 1907.

The background for this trip arose from the striking similarity of the thyroid hyperplasias of dogs, cattle and sheep as to both their morphology and their gradations in iodine store, together with a remark by Professor Torald Sollmann that clinicians had complained of the variable activity of commercial desiccated thyroid.

Through the courtesy of Mr. Bell, of the General Offices of Armour and

* Presented as the James D. Bruce Memorial Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 5, 1954.

Copyright, 1954, by The American College of Physicians

Company, I visited their laboratories and spent three very profitable hours with Dr. F. C. Koch (later a Distinguished Service Professor of Biochemistry).

On that particular day the workmen collecting sheep thyroids discarded about one third as "specs" (slaughterhouse slang), but according to our standard probably another third were somewhat enlarged.

Dr. Koch gladly supplied me with many samples of enlarged as well as normal sized glands, which I took back to Cleveland for histologic study and iodine determinations. He also sent me a generous supply of desiccated thyroid assaying 1.09 mg. iodine per gram of dried gland, which we used as our standard control for 38 years; and another sample made from goitrous glands which assayed 0.29 mg. iodine per gram dried. These two preparations when fed to dogs in daily doses of 600 mg. for 18 days had markedly different effects: the low iodine preparation had no noticeable effect, while the higher iodine preparation caused loss of body weight, diarrhea, increase in heart rate and iodine storage with rapid thyroid involution.[1] The data on the variable iodine content and physiologic activity of sheep and dog thyroids were brought to the attention of Professor Sollmann, a member of the Council on Pharmacy and Chemistry of the American Medical Association, and in whose laboratory Williams and I were working.

In 1908 Hunt and Seidell [3] reported their studies of commercial desiccated thyroid using the acetonitrile test. They found that the iodine content varied but the physiologic activity was proportional to the iodine content. Continuing their studies of desiccated thyroid they again concluded (1911) [2] that the pharmacologic activity of desiccated thyroid was proportional to its iodine content. They recommended a U.S.P. standard of 0.2 per cent, with a minimum of 0.17 and a maximum of 0.23 mg. per gram dried. A British firm had already fixed its standard at 0.2 per cent iodine. When thyroxine became available, Hunt [4] compared the protective action of thyroid with that of equivalent amounts of iodine as thyroxine given subcutaneously, and concluded that the activity of thyroid, iodine for iodine, was greater than thyroxine. This observation became still more striking after Harington (1926–27) [5a, 5b] had cleared up the chemistry of thyroxine, made it synthetically and showed that thyroxine accounted for less than 50 per cent of the total thyroid iodine. However, he suggested [6] that the thyroid might contain another compound with physiologic properties similar to those of thyroxine, but dismissed the possibility as too remote. The discrepancy between the activity of thyroid and thyroxine was confirmed by many workers, including Means and his group in Boston [7] and Thompson and his group in Chicago,[8] using myxedema patients. Their efforts to solve the mystery failed, and it was not until 1951 that Gross and Leblond [9] demonstrated, by means of chromatography, a new substance in the thyroid gland which they designated "Unknown 1." The following year Gross and Pitt-Rivers [10] and, independently, Roche, Lissitzky and Michel [11] identified

this substance as 3:5:3′ tri-iodothyronine. Studies in several laboratories [12] showed that this new substance was three to five times more active calorigenically than thyroxine; and thus a partial solution, at least, for the long-standing discrepancy between the activity of thyroid iodine and equivalent amounts of thyroxine iodine was at hand. The present day hypothesis,[10] that thyroxine may have to be enzymatically deiodinated in the tissues to become physiologically active, would suggest that incubated mixtures of serum or plasma and, thyroxine should be examined for tri-iodothyronine.

How the late Henry Plummer would have welcomed this contribution in support of his theory of incomplete thyroxine as the toxic factor in Graves's disease!

I have recited the highlights of one problem in thyroid chemistry and physiology only to illustrate the necessity and rewards of continuing biochemical research.

Getting back to our subject of endemic goiter again: The iodine content of large series of dog, pig, cattle and also fish thyroids was found generally to vary inversely with the degree of hyperplasia. All these animals' thyroids reacted similarly to the administration of iodine in all the forms we used, with storage and involution of the hyperplasias. The physiologic activity checked closely with the iodine store except in experiments where massive uptakes of iodine occurred within 24 hours before the thyroid specimens were taken.

All our animal series were from younger age groups, and there was a fairly uniform pattern of morphology, but when we tried to correlate these comparatively simple relations in animal thyroids with the morphology and iodine contents of series of human thyroids, both autopsy and surgical, we encountered difficulties. To be sure, a group of hyperplastic Graves's disease thyroids from Crile's clinic could be matched with the gradations of the animal series, but many of the Graves's disease glands and most of the so-called "colloid" and "nodular" goiters were too variable in morphology and iodine content to be correlated with the animal series.

We thought age and secondary morphologic changes might be factors, and we began experiments on the goitrous thyroids of old dogs. One of the dogs (A-106) was said to be 11 years old and had a large, palpably irregular goiter. On June 5, 1907, Lenhart and I removed one lobe weighing 29.5 gm. which contained many old scarred areas and hemorrhagic cysts, with scattered intact areas showing large irregular colloid filled follicles lined with flattened epithelium which we classified as "colloid goiter with multiple hemorrhagic cysts." After 40 days we removed approximately one-half of the remaining lobe, which weighed 15 gm. and was similar both grossly and microscopically to the first lobe removed. After 57 days we removed a portion of the remaining half lobe, which weighed 3 gm. Microscopically there were scarred areas, but the follicular epithelium, though irregular, was mostly columnar, and was classified as "moderately hyper-

plastic." A fourth specimen, removed 88 days later, weighed 4.5 gm. and was very vascular and soft. This we classified as "marked hyperplasia." This and other similar experiments established in our minds that compensatory hyperplasia in these long-standing and morphologically highly complex goiters was essentially identical with that observed by Halsted for normal thyroids of dogs. I think it was the most satisfying group of experiments we ever did. We now had a clue.[13] Physiologically *struma diffusa colloides* meant something, and *struma diffusa colloides proliferans* meant more. A morphologic cycle was established for colloid goiter identical with that for normal glands. Colloid goiter, however complex morphologically, could no longer be classified as a degeneration but must be looked upon as a physiologic resting stage, essentially comparable to a normal thyroid, and now known to be the result of a reduced output of thyrotropic hormone. We were able to classify and correlate a much larger group of the human autopsy and surgical thyroid material. We could establish a colloid series of hyperplasias and involutions as well as a normal series.

While the thyroid cycle thus established could have rendered much descriptive morphology obsolete, it is a fact that we never succeeded in convincing pathologists to substitute a physiologic for the descriptive morphologic terminology until Phillip Smith [14] in 1922 demonstrated that fresh anterior pituitary of the ox contained something which, when administered parenterally, caused thyroid hyperplasia, and that after the injections were stopped the thyroid returned to a normal appearance except for the increase in size. Since then colloid goiter generally has come to be regarded as the involuted stage of hyperplasia and not as a degenerative process.

The work on the thyroid hyperplasias of animals and their variations in iodine content led us to believe that they were compensatory to provide a larger blood filter to collect more iodine, and to look upon the various morphologic stages in simple goiter in man as the cyclic manifestations of a vast natural experiment in overlapping and recurrent thyroid hyperplasia and involution.

The term "simple goiter" was originally used as a collective abbreviation for endemic, epidemic and sporadic, and also to distinguish it sharply from Graves's disease; for it was obvious that no form of goiter was simple (easily understood), but surely Graves's disease is far more complex, and basically probably not thyroidal.

The modern era of the study of endemic goiter may be said to date from the use of iodine in the treatment of goiter by Coindet in 1820, but it received its greatest boost from the discovery of iodine as a normal constituent of the thyroid by E. Baumann in 1895.*

However, we are still trying to correlate observations recorded nearly 2,000 years ago with the over-all problem of endemic goiter.

* I recall asking Professor Theodore Kocher in 1913 why it was that no one had thought of examining the thyroid for iodine for 75 years after Coindet had demonstrated its therapeutic value. He replied with obvious feeling that this was not the fact; that he had asked the Department of Chemistry to examine thyroids for iodine but that they failed to find it.

One of these ancient observations, shared by many peoples independently, is the relation of the last Glacial period (expressed as snow or glacier water by ancient peoples) to the etiology of goiter. These ancient peoples did not know that glacier water contained very little iodine, but they were firmly convinced that water somehow was the cause of their goiter troubles. Endemic goiter occurs for the most part on soils (till) deposited or leached by the melting ice of the last Glacial period. Not enough study has been given to this phase of medical geology as a cause of the low iodine content of soils and water in these areas. Geologists tell us that there has been no major change in the configuration of the earth's surface since long before the Glacial age.

Present day glaciers are the remnants of the last ice age, and the most important goiter districts today—the Alps, Himalaya, Andes, Southern Alps of New Zealand, Canadian Rockies—are closely associated with these vestiges of Pleistocene times. North America provides the simplest and best known picture of the ice age, and here the goiter districts correspond closely to the areas of glaciation.

Glacial soils (till or glacial drift) have been subjected to intense leaching during deposition by the melting ice. However, intense leaching and erosion of any soil cause a loss of iodide. It has been suggested that the loss of iodide (which is extremely soluble) from such soils is further increased by the higher pH caused by the high calcium and magnesium content which is generally characteristic of these intensely goitrous and usually fertile soils. On the other hand, acid soils rich in humus (bogs, old lake beds) are more retentive of iodine.[15] Baumann and I found that the leaves of skunk cabbage (*Symplocarpus foetidus*) contained the highest iodine content of any fresh-water plants we examined. Shee [16] has emphasized the high calcium and magnesium content of the glacial soils in the endemic goiter area of central Ireland—one of the so-called paradoxes, where endemic goiter exists near the sea. Other so-called paradoxic endemic goiter districts, also glacial, occur around Puget Sound in the State of Washington, in British Columbia and in the Canterbury Plains of New Zealand. The exact rôle of calcium and magnesium in the etiology of endemic goiter is still unknown, although, as suggested by Boussingault [17] in 1831 and confirmed by most subsequent workers, they aid in its development.[18]

Our natural intake of iodine comes mainly from water, directly, or indirectly from food. Plants, both sea and land, have the capacity to concentrate iodine.[50] The amounts of iodine in sea air or rain water are usually insufficient to overcome the iodine deficiency in glacial soils.

I recall the interesting story of Pemberton Meadows, a narrow glacial valley in British Columbia, described to me in 1917 (reported by Keith, 1924 [19]) by Mr. John Ronayne, a very observing settler whose farm was about 30 miles below the face and in sight of the receding glacier. In this valley the incidence of goiter in man and domestic animals (sheep, pigs,

cattle, fowl) was nearly 100 per cent. The most recently deposited glacial soils appear to be the most favorable for goiter development.

As existing glaciers continue to recede and world population increases, more of these valleys will attract settlers and protection against goiter will be necessary. Fortunately, this may be accomplished easily and cheaply, as was demonstrated in 1917 in Pemberton Meadows.

Looked at from another angle, the classic studies by Chatin [20] (1852–55) of iodine distribution in soils and water in relation to goiter incidence, and the more recent extensive studies of McClendon and his collaborators [21] in the United States, of von Fellenberg [22] in Switzerland, of Reith [23] in Holland, of Hercus, Benson and Carter [24] in New Zealand, and many others, if plotted, would make a map of the more recent glacial soils and water as well as show the inverse ratio of iodine supply and goiter incidence.

There are apparent exceptions, but it has been said that the exceptions when explained may prove the rule. Thus the depth of the glacial deposit in a given region of endemic goiter is not uniform and often the underlying rock formations are exposed. This may partly explain the uneven incidence of goiter in such districts—for example, the high incidence in Signau and the low incidence in La Chaux de Fonds in Switzerland (von Fellenberg). There are areas where outcropping natural salt licks and springs contain enough iodine to protect the local inhabitants, as reported by Roulin [25] in 1825, and by Boussingault [26] in 1831 and 1833 in the glaciated upper Cauca River Valley of Colombia. There is the recent observation of Kimball [27] in the Kanawha River Valley of West Virginia, also glacial, where locally produced crude salt obtained from outcropping salt springs prevented goiter, but when it was replaced by highly purified salt, goiter began to appear. I have been unable to find accurate estimations of the iodine content of these crude salts.

There are the islands of Japan, where there should be much endemic goiter but actually there is very little, if any. This is attributed by McClendon [28] to the general use of seaweed and sea fish as food. There is the island of Formosa, with considerable endemic goiter. There is Portland, Oregon, where the incidence of goiter has increased since the city began using the water from the melting ice of Mt Hood. The thyroid weights of Icelandic natives [29] are among the lowest reported in man, although they live in an environment similar to that prevailing in the Glacial period. As pointed out by Harington, goiter is unknown among the Eskimos. Many more "exceptions" could be cited.

The essential cause of simple goiter centers around the requirements, normal and abnormal, for iodine; hence, one may conclude that endemic goiter is an iodine deficiency disease.*

* The idea that a deficiency of something could cause disease was not popular a hundred years ago, when *positive* factors generally were the ruling conception. Chatin's work was criticized partly because of this by Virchow,[30] St. Lager [31] and Hirsch.[32] Indeed, between 1905 and 1910 Lenhart and I frequently heard the criticism that it was difficult to conceive of a deficiency or absence of something causing something.

This view is not unanimously accepted, and the search for a positive goiter noxa in the soil and water of endemic goiter areas, though not promising, should continue. The deficiency of iodine may be relative or absolute, and may be divided into three groups, as follows:[33] Group 1 includes factors that increase the requirements of the body for the thyroid hormone, such as puberty, pregnancy, menopause, certain infections and intoxications, cold (seasonal variations in the iodine store, and incidence of goiter),[34] excess of certain substances in the diet, including fats, proteins, calcium and magnesium, and deficient oxidation (anemias, high altitudes).

Group 2 includes factors that interfere with the storage or utilization of an otherwise adequate iodine intake. In 1923 I included this group only as a possibility, since there was then no evidence that the ability of the thyroid to collect and store iodide or to produce the thyroid hormone was at fault. Since then great advances have been made, and it is now necessary to subdivide this group into three parts.

The first (2a) of these subdivisions began when Chesney, Clawson and Webster[35] showed that cabbage, when fed to rabbits as the sole article of diet, often caused goiter. Attempts to find the cause of cabbage goiter led to the thiocyanates. Bromides and chlorides have a slight but similar action which depends upon their interference with the ability of the thyroid cells to collect the traces of iodine normally brought to it by the blood. Raising the blood iodine level promptly cancels out this interference.

The second (2b) of these subdivisions began with the demonstration that sulfaguanidine[36] and the thioureas,[37, 38] when fed to rats, produced goiter. Astwood has designated this group of drugs as antithyroid because they block the thyroid hormone-producing mechanism and hence are not influenced by increasing the iodine uptake and lead rapidly to myxedema and cretinism. By their studies of this subgroup Astwood and his group have made outstanding contributions.[39]

The third (2c) of these subdivisions began when Stanbury and Hedge[40] in 1950 reported a seacoast family with four goitrous cretins and one normal child. The cretins had hyperplastic thyroids, and the authors showed by means of radioactive iodine that these hyperplastic cretin thyroids had the usual enormous capacity for collecting iodide but were unable to convert it into thyroid hormone (similar to thiourea effect). This cause of thyroid hyperplasia must be rare and, if it can be confirmed, would strongly suggest an inherent inability of the thyroid cells to utilize iodide and might well be included in Garrod's "inborn errors of metabolism."

Group 3 includes the absolute deficiencies in the iodine intake. It now seems adequately proved that, in districts where goiter is endemic, (1) the iodine content of the water, soils and foodstuffs grown on such soils is below normal requirements; (2) a low iodine intake will cause thyroid hyperplasia, and (3) 40 to 80 micrograms of iodine daily in man or 0.5 to 1 microgram daily in rats will prevent the occurrence of thyroid hyperplasia. Combinations of the various factors in the three groups necessarily

cause increased thyroid reactions, and when the association is with pregnancy it may lead to cretinism.

I believe we can account for endemic goiter and most of the reported instances of epidemic goiter as dependent upon a deficient iodine intake. The cases of sporadic goiter, heretofore an enigma, may possibly be partially accounted for by the newer factors referred to in group 2a, b and c.

Prevention

Goiter prevention has had phenomenal success in domestic animals. This success is due in part to the use of crude (iodine-containing) salt. Its application to human goiter, however (Switzerland excepted), has fallen far short of what could have been accomplished during the 34 years since completion of the first large-scale experiment in its prevention.

The method of prevention is based on supplying additional iodine to supplement an inadequate natural intake. Over the years many ways have been suggested and actually tried, but by far the simplest is that of incorporating some salt of iodine in edible salt. This is also the oldest (Boussingault [17] recommended it in 1831) as well as nature's large scale method. Some instances come to mind. Goiter is unknown in animals living in the sea. McCarrison [41] states that it was a folk saying in Chitral (a district of Kashmir) that families who could afford the luxury of salt were usually free from goiter. The use of crude sea salt (containing up to 0.7 mg. iodine per kilogram), when this was the only salt available, offered some protection. The use of certain natural salt deposits containing iodine, as reported by Roulin (1825) [25] and Boussingault (1831 and 1833) [17, 26] in the Department of Antioquia, Colombia, had prevented goiter for more than 200 years, whereas those using a low iodine salt from deposits in nearby Zipaquira showed a very high goiter incidence. Kimball [27] reported that goiter began to appear in the valley of the Kanawha River, West Virginia, when the use of the local crude salt was replaced by imported highly refined salt about 1900. Southern Michigan had a similar experience with sheep.[42] The salt deposits there are covered up to 600 feet with glacial till (boulder clay, sand and gravel), but there were natural salt springs used by the Indians and early settlers.* Extensive salt production from borings began about 1860, and highly refined salt did not come into general use until after 1880 (Cook).[43] Coincident with the use of refined salt, goiter in sheep became a serious problem and threatened to force the abandonment of this important industry. Thus, like adding vitamin B_1 to bread, we are forced to add iodine to refined salt, at least that portion destined for human consumption, and in the absence of the natural stabilizers in crude salt to add a protective agent as well.

* The Indians manufactured salt from the natural saltsprings on the Great Kanawha River in W. Va., on the Saline River in southern Illinois and also in southern Michigan, southeastern Ohio, northern Kentucky, northern New York and in other areas.

The low incidence of goiter among the Indians, early explorers and settlers in these districts was probably in part due to the use of crude iodine-containing salt.

Then there was the opposition of physicians and surgeons, notably the late Theodore Kocher, which was the logical result of the abuse of iodine in the treatment of endemic goiter. Also, opposition arose from Federal authorities and Public Health Services for the same reasons. These and many other objections were continued despite the observations of Boussingault and Roulin in Colombia, the experience of the Japanese with seaweed, and the controlled Akron experiment,[44] all of which had failed to show any serious untoward effects of such amounts of iodine in thousands of individuals. Boussingault (1833) pointed out that the treatment of goiter in Colombia with iodine had caused "de tres sérieux accidens," while the use of naturally iodized salt in the Province of Antioquia had maintained a "parfaitement constitués" people for more than 200 years.

This raises the question of "Jod-Basedow's disease," which dates back to Coindet (1820) and occurs particularly in association with nodular (adenomatous) goiter. This experience brought severe criticism both of iodine therapy and of Coindet himself. The description of the clinical symptoms in these cases as given by Gairdner in 1824 [45] could hardly be improved upon today, although Parry's account of Graves's disease was still unpublished.

In this country, in the 10 years following the large-scale goiter prevention experiment in Akron (1919), many kinds of iodine medication, including candies, tablets and chewing-gum, ran wild; and there occurred a rapid rise in the admission rates of most hospitals and clinics of the Great Lakes goiter district for what, in this country, was designated "adenomatous goiter with hyperthyroidism." This rise reached its peak in 1928–29, and since then has gradually fallen,[46, 47] largely, as I see it, because the cases of adenomatous goiter susceptible to the abuse of iodine medication have decreased and new cases of adenomatous goiter have been reduced by prevention.

These cases of hyperthyroidism (Jod-Basedow) have occurred for the most part in persons with long-standing adenomatous goiter (struma nodosa) in the age group 45 to 55, hence in districts of endemic goiter where the natural incidence of Graves's disease is low.

The most intense hyperthyroidism of this type that I have seen has been in rabbits. The first instance was one of Dr. Chesney's cabbage goiters. As was expected, the initial O_2 consumption was considerably below normal. Following the intraperitoneal injection of three 25 mg. doses of KI on consecutive days, the O_2 consumption nearly doubled in seven days, body weight fell from 2.63 kg. to 1.63 kg., and the animal died on the twenty-fifth day with the intense hyperthyroidism continuing to the end. Webster and Chesney [48] included this rabbit in their extensive studies of fatal as well as nonfatal hyperthyroidism in rabbits with cabbage goiter, and concluded that the intensity of the hyperthyroidism depended more on the size of the parenchymatous goiter than on the size of the excessive dose of iodine. In similar experiments in dogs with large parenchymatous goiters some

loss of body weight also occurs, but I have never observed a fatal outcome. Mr. John Ronayne in 1917 described a reaction in a goitrous sow, to which he had given a dose of iodine, that probably was a case of iodine hyperthyroidism. He states that she became very weak, lost much weight and developed diarrhea, but that she recovered in about three weeks, with disappearance of the goiter. Why rabbits and possibly other animals with large parenchymatous goiters and certain individuals with adenomatous goiter are susceptible to this flooding of the tissues with thyroid hormone and its ensuing hyperthyroidism is not known. Perhaps tri-iodothyronine may supply part of the answer, particularly if the deiodination of thyroxine is due to an enzyme [49] in the tissues whose activity might be increased in these longstanding, low iodine goiters.

At all events, the outstanding facts are that the administration of supplementary iodine in the form of natural or artificially iodized salt in concentrations not exceeding 1:100,000 has not produced any serious untoward effects, while the use of so-called therapeutic doses in certain individuals with goiter, where the uptake of iodine and the elaboration of hormone may be greatly increased, has caused serious effects.*

In conclusion, we have not achieved the degree of control of simple goiter and its serious consequences (cretinism and deaf mutism) in man that it would be reasonable to expect from past experience and our present knowledge of thyroid physiology and chemistry. In only one country (Switzerland) is goiter prophylaxis carried out in a manner that shows every promise of its ultimate eradication. The obstacles to extending endemic goiter prevention arise mainly from three sources: (1) economic, (2) political, and (3) social, and are therefore at present beyond the authority of a Public Health Service.

BIBLIOGRAPHY

1. Marine, D., and Williams, W. W.: The relation of iodine to the structure of the thyroid gland, Arch. Int. Med. **1**: 349, 1908.
2. Hunt, R., and Seidell, A.: The pharmacopeal standard for desiccated thyroid glands, Am. J. Pharm. **83**: 407, 1911.
3. Hunt, R., and Seidell, A.: Studies on thyroid—I, Relation of iodine to physiological activity of thyroid, Bull. No. 47, Hyg. Lab., U. S. Pub. Health and M. H. S., Washington, 1908.
4. Hunt, R.: The acetonitrile test for thyroid and some alterations of metabolism, Am. J. Physiol. **63**: 257, 1923.
5. (a) Harington, C. R.: Chemistry of thyroxine. II. Constitution and synthesis of desiodothyroxine, Biochem. J. **20**: 300, 1926.

* Since the dangers of Jod-Basedow are serious in endemic goiter regions with a high incidence of advanced adenomatous goiter, it would seem advisable to use (as Switzerland has) a conservative iodide supplement (1:100,000) rather than greater concentrations. This concentration should meet most of the peak iodine requirements, with the possible exception of pregnancy (maternal and fetal goiter), without endangering those with longstanding adenomatous goiter. Since it might require 50 years before all adenomatous goiters existing at the beginning of goiter prophylaxis were naturally eliminated, limited surveys every 10 years for possible adjustments of the iodine supplement would be desirable.

(b) Harington, C. R., and Barger, G.: Chemistry of thyroxine. III. Constitution and synthesis of thyroxine, Biochem. J. **21**: 169, 1927.
6. Harington, C. R.: The thyroid gland, 1933, Oxford University Press, London.
7. Means, J. H., Lerman, J., and Salter, W. T.: The role of thyroxine iodine and total organic iodine in the calorigenic action of whole thyroid gland, J. Clin. Investigation **12**: 683, 1933.
8. Thompson, W. O., McLellan, L. L., Thompson, P. K., and Dickie, L. F. N.: The rates of utilization of thyroxine and of desiccated thyroid in man: the relation between the iodine in desiccated thyroid and in thyroxine, J. Clin. Investigation **12**: 235, 1933.
9. Gross, J., and Leblond, C. P.: The presence of free iodinated compounds in the thyroid and their passage into the circulation, Endocrinology **48**: 714, 1951.
10. Gross, J., and Pitt-Rivers, R.: The identification of 3:5:3′ l-triiodothyronine, Lancet **1**: 439, 1952.
11. Roche, J., Lissitzky, S., and Michel, R.: Sur la triiodothyronine, produit intermediaire de la transformation de la diiodothyronine en thyroxine, Compt. rend. Acad. d. sc. **234**: 997, 1952.
12. Asper, S. P., Jr., Selenkow, H. A., and Plamondon, C. A.: A comparison of the metabolic activities of 3:5:3′ l-triiodothyronine and l-thyroxine in myxedema, Bull. Johns Hopkins Hosp. **93**: 164, 1953.
13. Marine, D., and Lenhart, C. H.: Colloid glands (goitres): their etiology and physiological significance, Bull. Johns Hopkins Hosp. **20**: 131, 1909.
14. Smith, P. E., and Smith, I. P.: The repair and activation of the thyroid in the hypophysectomized tadpole by the parenteral administration of fresh anterior lobe of the bovine hypophysis, J. M. Research **43**: 267, 1922.
15. von Fellenberg, Th.: Ueber das Verhalten saurer und alkalischer Böden im Joddungungsversuch, Biochem. Ztschr. **188**: 326, 1927.
16. Shee, J. C.: Problem of endemic goiter in Ireland, Irish J. M. Sc. pp. 752, 802, 1939.
17. Boussingault, J. B.: Recherches sur la cause qui produit le goitre dans les Cordilieres de la Nouvelle Grenade, Ann. de Chim. et Phys. **48**: 41, 1831.
18. Thompson, J.: Influence of the intake of calcium on the thyroid gland of the albino rat, Arch. Path. **16**: 211, 1933.
19. Keith, W. D.: Endemic goiter, Canad. M. A. J. **14**: 284, 1924.
20. Chatin, A.: Recherche de l'iode dans d'air, les eaux, le sol et les produits alimentaires des Alpes de la France et du Piemont, Compt. rend. Acad. d. sc. **34**: 14, 51, 409, 1852.
21. McClendon, J. F.: The distribution of iodine with special reference to goiter, Physiol. Rev. **7**: 189, 1927.
22. von Fellenberg, Th.: Untersuchungen über das Vorkommen von Jod in der Natur. I, Biochem. Ztschr. **139**: 371, 1923.
23. Reith, J. F.: Ueber den Jodgehalt der Atmosphaere in Holland, Biochem. Ztschr. **260**: 115, 1933.
24. Hercus, C. E., Benson, W. N., and Carter, C. L.: Endemic goitre in New Zealand and its relation to the soil iodine, J. Hyg. **24**: 321, 1925.
25. Roulin: Sur quelques faits relatifs a l'histoire des goitres, J. Physiol. (Magendie) **5**: 266, 1825.
26. Boussingault, J. B.: Memoire sur les salines iodiferes des Andes, Ann. de Chim. et Phys. **54**: 163, 1833.
27. Kimball, O. P.: History of the prevention of endemic goitre, Bull. World Health Organization **9**: 241, 1953.
28. McClendon, J. F.: Iodine and goiter with special reference to the Far East, J. Biol. Chem. **102**: 91, 1933.
29. Sijurjonsson, J.: Studies on the human thyroid in Iceland, Monograph, Reykjavik, 1940, Lewis, London.
30. Virchow, R.: Die Krankhafte der Geschwülste, 1863, A. Hirschwald, Berlin.

31. St. Lager, J.: Etudes sur les causes du crétinisme et du goitre endemique, 1867, J. Bailliere et fils, Paris.
32. Hirsch, A.: Kropf und Cretinismus, *in* Handb. der historisch-geographischen Pathologie, 1883, F. Enke, Stuttgart.
33. Marine, D.: The importance of our knowledge of thyroid physiology in the control of thyroid diseases, Arch. Int. Med. **32**: 811, 1923.
34. Seidell, A., and Fenger, F.: Seasonal variation in the iodine value of the thyroid glands, J. Biol. Chem. **13**: 517, 1913.
35. Chesney, A. M., Clawson, T. A., and Webster, B.: Endemic goiter in rabbits: I. Incidence and characteristics, Bull. Johns Hopkins Hosp. **43**: 261, 1928.
36. Mackenzie, C. G., and Mackenzie, J. B.: Effects of sulfonamides and thioureas on the thyroid gland and basal metabolism, Endocrinology **32**: 185, 1943.
37. Richter, C. P., and Clisby, K. H.: Toxic effects of bitter tasting phenylthiocarbamide, Proc. Soc. Exper. Biol. and Med. **48**: 684, 1941.
38. Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: Action of certain sulfonamides and of thiourea upon the function of the thyroid gland of the rat, Endocrinology **32**: 210, 1943.
39. Astwood, E. B.: Natural occurrence of antithyroid compounds as a cause of simple goiter, Ann. Int. Med. **30**: 1087, 1949.
40. Stanbury, J. B., and Hedge, A. N.: A study of a family of goitrous cretins, J. Clin. Endocrinol. **10**: 471, 1950.
41. McCarrison, R.: Etiology of endemic goitre (Milroy Lectures), 1913, J. Bale, Sons and Danielsson, London.
42. Marine, D.: On the occurrence and physiological nature of glandular hyperplasia of the thyroid (dogs and sheep) together with remarks on important clinical (human) problems, Bull. Johns Hopkins Hosp. **18**: 359, 1907.
43. Cook, C. W.: The brine and salt deposits of Michigan, Thesis, University of Michigan, Ann Arbor, 1914.
44. Marine, D., and Kimball, O. P.: The prevention of simple goiter in man, Arch. Int. Med. **25**: 661, 1920.
45. Gairdner, W.: Essay on the effects of iodine on the human constitution, etc., 1824, T. and G. Underwood, London.
46. Plummer, H. S.: Exophthalmic goiter in Olmsted County, Minnesota, Tr. A. Am. Physicians **46**: 171, 1931.
47. McClure, R. D.: Thyroid surgery as affected by the generalized use of iodized salt in an endemic goiter region—preventive surgery, Ann. Surg. **100**: 924, 1934.
48. Webster, B., and Chesney, A. M.: Endemic goiter in rabbits. III. Effects of administration of iodine, Bull. Johns Hopkins Hosp. **43**: 291, 1928.
49. Gross, J., and Pitt-Rivers, R.: Physiological activity of 3:5:3′ l-triiodothyronine, Lancet **1**: 593, 1952.
50. Orr, J. B., and Leitch, I.: Iodine in nutrition: a review of existing information, 1929, H. M. Stationery Office, London, p. 108.

PERIARTERITIS NODOSA: RECOGNITION AND CLINICAL SYMPTOMS *

By M. A. Blankenhorn, M.D., F.A.C.P., and Harvey C. Knowles, Jr., M.D., *Cincinnati, Ohio*

Introduction

In order to discuss briefly the recognition and the clinical symptoms of periarteritis nodosa it is a primary necessity to formulate some definitions and a scheme of classification. I have been much helped with this problem by a pathologist who has been studying it for more than 20 years at the Cincinnati General Hospital. I refer to Dr. Pearl Zeek, our Associate Professor, and I quote her now: [1]

"The concept that all the conditions in which there are vascular lesions characterized by fibrinoid necrosis and inflammatory reaction constitute one pathologic entity becomes untenable when the wide variety of experimental procedures, that have given rise to the lesions in animals, are considered and when attention is focused upon the differences in morphology and in the distribution of the lesions in man."

Her analysis [2] of autopsy and biopsy material of about 60 patients in our own and associated hospitals has suggested the following clinical classification with the general name "necrotizing angiitis" to designate the lot (table 1). For this consideration I shall restrict myself even more by ignoring the very infrequent forms, i.e., classes 3 and 4. There then remain 45 patients, most of them seen by myself or my associates (table 2).

This leaves us three groups in which typical vascular lesions were found at autopsy or biopsy, and of these the largest group (21) are classed as secondary periarteritis nodosa because they were all people who died as a result of hypertensive renal disease and periarteritis nodosa, or necrotizing angiitis was discovered in an exceptionally wide search of the small arteries. Pathologically, they were periarteritis nodosa of short duration, but clinically they were severe renal disease with hypertension. We will dismiss this group of 21 with no more words than to say that hypertensive renal disease is probably an etiologic factor in periarteritis nodosa.

Our chief concern now, for this report, resides in 14 patients who had at autopsy the typical Kussmaul-Maier type, and 10 others who had hypersensitivity angiitis of the Zeek type, if you will.

If, now, this is thought to oversimplify the task, we could put all the

* Presented at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 5, 1954.

From the Department of Internal Medicine, College of Medicine, University of Cincinnati, and the Department of Medicine, Cincinnati General Hospital, Cincinnati, Ohio.

more than a thousand collected and isolated case reports through an analysis for clinical correlations, but this has been done repeatedly without developing any acceptable theory as to primary causes or any better system of diagnosis than the one we use, namely, to be suspicious at the right time and examine by biopsy a suitable material. In recent times (1950 to date), case reporting is largely of the new and bizarre forms, so it appears that almost any tissue which has arteries, capillaries and veins can have typical lesions and the lesions be associated with almost any disease, such as dis-

TABLE 1

The Necrotizing Angiitides

1. Periarteritis Nodosa
2. Hypersensitivity Angiitis
3. Rheumatic Arteritis
4. Temporal Arteritis
5. Allergic Granulomatous Angiitis

seminated lupus, dermatitis herpetiformis, sarcoidosis, Felty's, Reiter's, Wegener's and Cogan's [3] syndromes. Also, many drugs other than foreign serum and sulfonamides have been implicated, such as mercurial diuretics, hydantoin,[4] thiouracil, penicillin and other drugs producing purpura or hemolytic anemia supposedly by causing hypersensitivity.

Therefore, I think best to find our clinical correlations in a more thorough study at one place by one group of workers. The pathologic classifications were made by Dr. Zeek. Dr. Harvey Knowles, of the De-

TABLE 2

Necrotizing Angiitis at the Cincinnati General Hospital
General Aspects

	Periarteritis Nodosa	Secondary Periarteritis Nodosa	Hypersensitivity Angiitis
No. of Cases	14	21	10
Sex: M/F	13/1	12/9	8/2
Hist. Allergy	1	0	0
Hist. of Sulf.	0	2	7
Hypertension	10/12	21	3
Duration	5–52 wk.	xxxxx	6–32 days

partment of Medicine, made the clinical classifications but did so independently, that is, without knowing any more than the basic diagnosis (necrotizing angiitis). By this device we have avoided the fallacy of making an arbitrary grouping and then looking upon it as a natural phenomenon. In almost every instance they were in agreement.

The pathology, gross and microscopic, of the two remaining groups is set forth in table 3 and can be summarized in this manner: In periarteritis nodosa, small and medium sized arteries of the muscular type are involved; in hypersensitivity angiitis, arterioles, venules, capillaries and small arteries are also involved. The location of the lesions of periarteritis nodosa is in

TABLE 3

Pathology of Periarteritis Nodosa and Hypersensitivity Angiitis

	Periarteritis Nodosa	Hypersensitivity Angiitis
Vessels Involved	Small and medium sized arteries. Muscular type	Arterioles, venules, capillaries. Small arteries
Location of Lesions	Branchings in hilar regions of viscera. Muscle	Within viscera and interstitial tissues
Characteristics of Lesions	Various ages. Proliferation precedes exudation in the adventitia. Forms granulation tissue and small aneurysms	All of about same age. Exudative reaction
Associated Lesions	Sequelae of vascular obstruction and hypertension	Visceral interstitial inflammation. Necrotizing glomerulonephritis. Fibrinoid pneumonia

the branches of the small arteries at the hilus of a viscus and is common in muscle. The lesions in hypersensitivity angiitis are located within the viscera and interstitial tissue. Characteristically, various ages of the lesions of periarteritis nodosa are present at one time. Proliferation precedes exudation. There is granulation tissue. Small aneurysms occur. The lesions of hypersensitivity angiitis are characterized by their being all of about the same age and having exudative reaction. Associated lesions of hypersensitivity angiitis are visceral interstitial inflammation, necrotizing glomerulonephritis, and fibrinoid pneumonia.

The clinical expression of these specific lesions is determined by their location in various organ systems and in individual organs or parts of organs. If periarteritis is indeed a clinical entity, it must be as a multiple system disease. The basis of this clinical aphorism is seen in table 4.

Table 4 gives the distribution of lesions in these two contrasted diseases as arranged in organ systems. The organs are arranged in the order of the frequency of the lesions of periarteritis nodosa. The kidney was involved

TABLE 4

Distribution of Lesions at Autopsy

Location	Periarteritis Nodosa		Hypersensitivity Angiitis	
	No. Exam.	No. Positive	No. Exam.	No. Positive
Kidney	14	14	10	10
Gastroenteric Tract	13	13	7	3
Heart	14	13	10	4
Pancreas	12	11	10	1
Liver	14	11	10	7
Gall-bladder	9	9	2	1
Muscle	8	8	4	0
Peripheral Nerves	7	6	0	?
Spleen	14	2	10	7
Lungs	14	0	10	4

in both conditions in all our cases. The gastroenteric tract, the heart and the pancreas were involved much more frequently in periarteritis nodosa than in hypersensitivity angiitis. The spleen and the lungs were seldom involved in periarteritis nodosa but were frequently involved in hypersensitivity angiitis.

In a previous publication [2] a very complete tabulation of clinical and pathologic items was made and need not be printed again. Only the trends are shown here.

I will again dismiss secondary polyarteritis nodosa as an end stage of hypertensive renal disease and summarize the clinical aspects of primary periarteritis nodosa and hypersensitivity angiitis. There is a notable contrast in that eosinophilia was very common in periarteritis nodosa and rare in hypersensitivity angiitis. The lungs were not involved in periarteritis nodosa but were occasionally involved in hypersensitivity angiitis. The gastroenteric tract was involved frequently in periarteritis nodosa and rarely (see table 4) in hypersensitivity angiitis. There was a high incidence of hematuria in both groups. Clinical uremia was absent from the periarteritis nodosa but was common in the hypersensitivity angiitis group. Clinical uremia was almost the rule in secondary periarteritis nodosa. Peripheral neuritis was very common in periarteritis nodosa, absent from hypersensitivity angiitis.

It is somewhat presumptuous to offer any of the above as new or very different in the way of clinical experience, unless it be our emphasis on the differentiation between hypersensitivity angiitis and the traditional periarteritis nodosa, and our emphasis on kidney disease and severe hypertension as causative factors in the one and drug sensitivity in the other. To lump all the forms that are described into the basket with collagen disease has not, in our experience, added greatly to our understanding. In our series there are three cases coincidental with disseminated lupus and one combined with rheumatoid arthritis, but in all the rest there was no confluence with skin, joint or connective tissue diseases, such as arthritis, periarthritis or scleroderma. In two of our hypersensitivity angiitis cases there were joint symptoms suggestive of rheumatic fever.

We have reported no study heretofore on anything but autopsy material. The natural course of periarteritis nodosa in either form we do not know. In the clinic we have made the diagnosis three times, as confirmed by biopsy in patients still living.

We have no firm views about treatment. Dr. Zeek has had tissue sent to her that showed well healed lesions in arteries that were completely obstructed by the healing process. These patients had been treated with ACTH and with cortisone. Other workers have reported good results [5] and still others bad results from this same treatment.[6]

As to acute hypersensitivity angiitis, there are case reports of critical improvement with treatment, but all of our patients died. From the nature of

the lesions of periarteritis nodosa one would expect worsening if any form of treatment increased the hypertension and led to the infarction of vital organs. Hypersensitivity angiitis, on the other hand, if recognized early as a sensitivity reaction, might be remarkably improved. We have not been fortunate enough to recognize the disease in time for that.

The recognition of classic periarteritis nodosa depends on one's being alert to the problem. The Medical Service in the Cincinnati General Hospital has been very alert and takes numerous negative muscle biopsies. Of six patients so diagnosed, the biopsy of a muscle was positive five times. On several occasions the first biopsy was negative and the second positive—probably because a larger specimen was taken.

No biopsy was made of any patient with hypersensitivity angiitis because the disease was usually fulminant and not recognized.

One patient with typical periarteritis nodosa has had spontaneous remission for four years but meanwhile is being treated for Pott's disease. A second patient, who was treated mostly with salicylates, had remission for six months and then relapsed fatally.

Summary

Forty-five cases of necrotizing angiitis (fibrinoid necrosis and inflammatory reaction in vessel walls) seen at the Cincinnati General Hospital were divided pathologically into two groups, namely, classic periarteritis nodosa and hypersensitivity angiitis. Certain striking differences in course and symptomatology were revealed. It was found that cases of periarteritis nodosa were divisible clinically into two groups, which were designated primary and secondary periarteritis nodosa, the only differences in the morphology of the lesions being those attributable to variations in the duration and extent of the pathologic process.

The 14 cases designated primary periarteritis nodosa presented widespread lesions in various stages, at necropsy, after a long clinical course characterized by gastroenteric symptoms, peripheral neuropathy, usually hypertension and occasionally eosinophilia. Twenty-one cases of secondary periarteritis nodosa were essentially cases of renal disease with hypertension, in which a few lesions of periarteritis nodosa had been initiated a short time before death. In these the clinical findings of periarteritis nodosa were masked by those of severe renal disease and hypertension.

In sharp contrast, the 10 cases of hypersensitivity angiitis were manifested clinically as a fulminant disease characterized by fever, skin rash, nephritis, myocarditis and, frequently, a history suggesting recent exposure to some antigenic substance.

It is suggested that periarteritis nodosa and hypersensitivity angiitis can be differentiated clinically and that they represent two distinct disease conditions.

BIBLIOGRAPHY

1. Zeek, P. M.: Medical progress, periarteritis nodosa and other forms of necrotizing angiitis, New England J. Med. **248**: 764–772 (Apr. 30) 1953.
2. Knowles, H. C., Jr., Zeek, P. M., and Blankenhorn, M. A.: Studies on necrotizing angiitis. IV. Periarteritis nodosa and hypersensitivity angiitis, Arch. Int. Med **92**: 789–805 (Dec.) 1953.
3. Oliner, L., Taubenhaus, M., Shapira, T. M., and Leshin, N.: Nonsyphilitic interstitial keratitis and bilateral deafness (Cogan's syndrome) associated with essential polyangitis (periarteritis nodosa), New England J. Med. **248**: 1001–1008, 1953.
4. Frankel, A. L., and Rothermich, N. O.: Polyarteritis nodosa: review together with report of case due to hydantoin sensitization treated with cortisone, Ohio State M. J. **47**: 1013–1021, 1951.
5. Shick, R. M., Baggenstoss, A. H., Fuller, B. F., and Polley, H. F.: Effects of cortisone and ACTH on periarteritis nodosa, Minnesota Med. **34**: 852–853, 1951.
6. Fahrlander, H.: Uber Periarteriitis nodosa, Schweiz. med. Wchnschr. **83** (Pt. 1): 575–577, 1953.

OSTEOMALACIA IN NEW YORK*

By I. Snapper, M.D., *Brooklyn, N. Y.*, R. Seely, M.D., S. Falk, M.D., *New York, N. Y.*, and I. Feder, M.D., F.A.C.P., *Brooklyn, N. Y.*

Osteomalacia, the adult counterpart of rickets, is generally considered a rarity in the western world, since avitaminosis D, the commonest cause of the disease, is thought to occur only in regions where exposure to sunshine is scarce and dietary deficiency and malnutrition are common.

In this part of the world osteomalacia is practically limited to conditions where vitamin D is not absorbed from the intestine. Malabsorption of fat-soluble vitamin D occurs in the chronic fatty diarrhea which is present in the sprue syndrome, in chronic biliary obstruction, and in long-standing obstruction of the pancreatic ducts. In the sprue syndrome, the absorptive powers of the small intestine are impaired; in pancreatic disease, the absence of lipase prevents the hydrolysis of neutral fats which is necessary for fat absorption. In chronic biliary obstruction the bile acids, important factors for the absorption of fats, cannot reach the lumen of the small intestine. In one of our patients sclerodermatous changes of the intestinal wall apparently prevented the absorption of fat and fat-soluble substances, among them vitamin D. Patients with long-standing steatorrhea are usually debilitated, and since they do not expose themselves regularly to sunshine no vitamin D can be formed in the skin. The combination of malabsorption of vitamin D and lack of formation of this vitamin results in avitaminosis D.

The following cases seen at various hospitals in New York City during the past years illustrate the occurrence of osteomalacia in association with disturbances of the absorption of fats and fat-soluble substances from the gastrointestinal tract.

Case Reports

Case 1. A 32 year old housewife was admitted on July 10, 1952, complaining of severe pain in the hips of five months' duration.

The patient had been well until one and one-half years before admission when, during the second trimester of her first pregnancy, she noted swelling of both legs. This cleared quickly following a mercurial injection. Thereafter she required occasional mercurial injections to control the swelling of the legs. There was no excessive weight gain and no hypertension, and she had a normal delivery in the ninth month. Throughout the pregnancy the appetite remained good and her diet contained adequate quantities of meat, fresh vegetables, fruits and a quart of milk daily, along with calcium supplements. She did not nurse her infant.

Three months after the end of the pregnancy she began to feel pain in both hips. Her physician told her that she had "a fracture of the pelvis" and advised her to drink as much milk as possible. The pain was progressive, however, and became so disabling that a short time prior to admission she was forced to use crutches.

* Received for publication May 24, 1954.

Two and one-half months before admission she had a severe attack of vomiting, accompanied by watery, non-bloody diarrhea. This was treated at home with intravenous fluids. Swelling of the legs recurred for the first time since the end of the pregnancy, and mercurial injections were administered again. As the episode of diarrhea subsided a change in bowel habit occurred. Instead of one daily, well-formed movement, she now had three to four loose or semi-formed movements a day. These were never bloody, bulky or frothy. There was no nausea, vomiting or abdominal pain. One month before admission she was given a two week course of cortisone, 75 mg. per day, without a change in bowel symptoms. Amenorrhea was present for two months before admission. For several months she had noted frequent spontaneous ecchymoses over the legs.

Physical examination disclosed an underdeveloped, pot-bellied woman with signs of marked weight loss. The blood pressure was 105/60 mm. of Hg. The temperature was normal. Both heart and lungs were unremarkable. The abdomen was slightly distended and tympanitic, with active bowel sounds. No viscera or masses were palpated. There was a moderate dorsal kyphosis without tenderness to percussion. Marked tenderness was present over the iliac crests, the coccyx, the lower ribs and the heads of the femora. The skin over the dorsum of both feet was slightly thickened and bound down to the subcutaneous tissue. The skin of the legs from the knee to the ankle was thickened, reddened and slightly tender. There was some puckering of the skin about the mouth.

The hemoglobin was 6.0 gm.; red cell count, 2,860,000; white cell count, 3,400, with a normal differential. A sternal marrow aspiration revealed a normally active marrow with an adequate number of megakaryocytes. No tumor or myeloma cells were seen. The urine was acid in reaction and otherwise unremarkable. The sedimentation rate was 28 mm. in one hour. The fasting blood sugar was 80 mg. per cent; the blood urea nitrogen, 18 mg. per cent; serum albumin, 3.1 gm. per cent; serum globulin, 1.9 gm. per cent; cholesterol, 140 mg. per cent, with esters of 95 mg. per cent. The CO_2 combining power was 51 vol. per cent, and the serum chloride, 106 mEq./L. The prothrombin time was 33.5 seconds, with a control time of 14 seconds.

The following abnormal values significant for the diagnosis of osteomalacia were obtained:

The serum calcium was 8.8 mg. per cent; the serum phosphorus, 1.3 mg. per cent, and the alkaline phosphatase, 32 King-Armstrong units. Several casual urine specimens gave a negative Sulkowitch reaction. On a Bauer-Aub test diet the 24-hour calcium excretion in the urine was low—98 mg. Examination of the stool revealed 58 per cent fat by dry weight, with 36 per cert neutral fat and 22 per cent fatty acids. The fasting vitamin A level of the serum was 12 gamma per cent. A vitamin A tolerance test showed a flat curve (four hours, 22 gamma per cent; six hours, 14 gamma per cent, and eight hours, 20 gamma per cent).

A gastrointestinal series, including examination of the small bowel, revealed no abnormality. Barium enema was unremarkable. Roentgen examination of the skeletal system disclosed severe demineralization involving the entire spine, skull and pelvis. A lesser degree of demineralization was noted in the extremities (figure 1).

Old symmetrical fractures were present through both pubic bones near their junction with the ischiatic arches (figure 2). The hands showed moderate subperiosteal resorption of bone in the middle phalanges.

The biochemical syndrome, consisting of decrease of calcium and phosphorus content of the serum, and increase of alkaline phosphatase and hypocalciuria, was typical for osteomalacia. So was the x-ray picture of the skeleton, with the fractures of the pubic bones and the thinning of the cortex of several parts of the skeleton. In this patient whose vitamin D intake was satisfactory, osteomalacia could have

FIG. 1. *Case 1.* Scleroderma and osteomalacia. Demineralization of tibia with lamellation of cortex. Looser zone in fibula.

resulted only from an insufficient absorption of fat-soluble substances. The high fat content of the stool, the prolonged prothrombin time and the flat vitamin A tolerance curve all pointed to the presence of a disturbance of the intestinal absorption of fat. The condition of the skin of the legs and feet was highly suggestive of scleroderma. This clinical impression was confirmed by a biopsy of the skin of the

FIG. 2. *Case 1.* Scleroderma and osteomalacia. Severe demineralization of pelvis with pathologic fractures of junction of both pubic zones with ischial arches.

legs, which was reported as "focal atrophy and fibrosis of papillae with flattening of the epidermis—the histology of scleroderma." Although no x-ray changes of the small intestine could be elicited, it seemed highly probable that the fat absorption was embarrassed by scleroderma of the small intestine and perhaps also of the mesenteric lymph nodes.

To improve this spruelike syndrome with associated osteomalacia, the patient was given 200,000 USP units of vitamin D (Hideratol) intramuscularly each day, and also daily ultraviolet radiation. The urine Sulkowitch reaction, which had been consistently negative, became positive five days after treatment was begun. At the end of two weeks, on a repeat Bauer-Aub diet, 180 mg. of calcium were excreted in the urine in 24 hours. During this time there was a gradual lessening of pain in the hips, so that by the end of her hospital stay the patient was able to discard her crutches.

Vitamin K was given parenterally and reduced the initially prolonged prothrombin time to normal within four days. Folic acid was also given, but without any change in bowel complaints at the time of discharge. At the time of discharge from the hospital after four weeks the serum calcium was 8.3 mg. per cent, the serum phosphorus had risen to 2.7 mg. per cent, and the alkaline phosphatase was 46 King-Armstrong units.

In November, 1953, the condition of the skeleton apparently was better, since the bone pains had completely disappeared and the patient could move around freely. Unfortunately, the scleroderma had progressed considerably. The skin of the lower extremities was very thin and tense. Several neurotrophic ulcers had developed upon the dorsum of the feet which seriously hampered the patient in her daily activities.

She had gradually stopped the ultraviolet treatment and the vitamin D administration. This may be one of the reasons why, in January, 1954, she suffered a fracture of the leg.

Case 2. A 56 year old merchant was first admitted on March 11, 1946, with a history of upper abdominal pain and low grade fever of several weeks' duration.

Physical examination disclosed moderate right upper quadrant tenderness and a palpable mass below the right costal margin. There was no icterus. The urine contained no bile and the urobilinogen was 1:40. Serum bilirubin was 0.6 mg. per cent; alkaline phosphatase, 61 King-Armstrong units; cholesterol, 360 mg. per cent, with esters of 250 mg. per cent. The cephalin flocculation test was 1 plus. The high alkaline phosphatase content of the serum in the absence of clear-cut jaundice needs special comment. It indicated that, irrespective of the presence of extrahepatic obstruction, a considerable degree of intrahepatic obstruction in the form of cholangiolitis was already present.

Soon after admission the patient had a chill, the temperature rose to 104° F., and icterus appeared. A blood culture revealed *Escherichia coli.* At laparotomy the gall-bladder was found to be distended and acutely inflamed, and contained many calculi and a large quantity of yellow pus. The common duct contained frank pus, but probing failed to reveal any calculi. T-tube drainage was instituted, and postoperatively icterus began to fade. The T-tube was removed at the end of three weeks, and the patient was discharged in good condition.

During the next six months he had four attacks of chills, fever and transient icterus, each lasting several days. In September, 1946, jaundice recurred and he was admitted to the Lahey Clinic, where on exploration of the common duct gravel was found and removed. Laboratory findings on this admission were: serum bilirubin, 3 mg. per cent; alkaline phosphatase, 38 Bodansky units; cholesterol, 245 mg. per cent, with esters of 165 mg. per cent; serum albumin, 3.0 gm. per cent; globulin, 5.2 gm. per cent, and cephalin flocculation test, 1 plus. The hyperglobulinemia apparently indicated the presence of liver damage, probably due to cholangitic or biliary liver cirrhosis. Following this second operation icterus failed to clear.

The patient was re-admitted to Mt. Sinai Hospital on August 29, 1947, for reevaluation and possible further surgery. Physical examination disclosed a poorly nourished male with deep icterus. Xanthelasmata were noted for the first time.

The liver was palpable four fingerbreadths below the right costal margin and was very firm, smooth and nontender, with a sharp edge. The spleen was not palpable. The remainder of the examination was unrevealing. The hemoglobin was 13 gm.; white cell count was 6,700, with a normal differential. The urine contained 3 plus bile and 1 : 30 urobilinogen. The stool contained stercobilin and was guaiac-negative. The serum bilirubin was 5.0 mg. per cent; alkaline phosphatase, 37 King-Armstrong

FIG. 3. *Case 2.* Biliary or cholangitic cirrhosis with superimposed osteomalacia. Demineralization of spine with fracture and wedging of fifth thoracic vertebra.

units; cholesterol, 540 mg. per cent, with esters of 260 mg. per cent. The cephalin flocculation test was negative. The common duct was again explored operatively and was found to contain a large quantity of pasty material. T-tube drainage resulted in decreasing icterus, improved appetite and a fall in the serum alkaline phosphatase to 19 King-Armstrong units, the serum cholesterol to 320 mg. per cent.

During the next three years the patient was seen at intervals by his own physician. He showed an indolent downward course of progressive biliary cirrhosis.

In the spring of 1950 he began to complain of pain in the spine. X-rays of the skeletal system then revealed marked generalized demineralization. There was a pathologic fracture through the upper part of the second sacral segment of the spine, and the body of the fifth dorsal vertebra showed marked wedging (figure 3). Irregular fractures were seen in the posterior portion of the left sixth rib, the anterior portion of the left fifth rib, through the clavicle, and there was an irregular depressed

FIG. 4. *Case 2.* Biliary or cholangitic cirrhosis with superimposed osteomalacia. Pathologic fracture of sternum.

fracture through the midportion of the sternum (figure 4). At this time the serum calcium was 11 mg. per cent; serum phosphorus, 3.9 mg. per cent, and alkaline phosphatase, 35 King-Armstrong units. He then received treatment with ultraviolet light and injections of vitamin D. This resulted in rapid improvement of the bone pains.

He was admitted for the last time on September 22, 1950, in a state of far advanced biliary cirrhosis, with deep icterus, fetor hepaticus, marked ascites and semi-

coma. Coma deepened rapidly and he died two weeks after admission. No postmortem examination was obtained.

Case 3. A 46 year old white male was admitted on February 7, 1952, complaining of weakness and fainting spells.

In 1937 the patient had first noted abdominal cramps and diarrhea with blood and mucus in the stool, and a diagnosis of ulcerative colitis was made. In 1944 he was seen at the Mayo Clinic, where he was found to have far advanced ulcerative colitis with nutritional edema. Proctoscopic examination showed a marked stricture at 18 cm. In view of impending obstruction, intractable diarrhea and marked wasting, an ileostomy was performed. In 1945 the terminal ileum and the colon from cecum to proximal descending portion were removed.

He was not seen again until November, 1949, when he returned to the Mayo Clinic with a three weeks' history of icterus. On examination marked ascites was present. Laboratory findings disclosed that the total serum protein was 5.8 gm. per cent, with a reversed albumin-globulin ratio, the cephalin flocculation test was 3 plus, and the alkaline phosphatase was 5.1 Bodansky units. A diagnosis of subacute infectious hepatitis was made and the patient was treated with a high protein, high carbohydrate diet with vitamin supplements. The icterus and ascites cleared slowly under this regimen.

In February, 1952, he had a convulsive seizure with loss of consciousness lasting about 20 minutes, for which he was admitted to the Beekman Downtown Hospital. On examination he was emaciated and markedly jaundiced. A firm liver edge was palpable several fingerbreadths below the right costal margin. An ileostomy opening was present in the right lower quadrant just to the right of the midline. There was no surrounding tissue breakdown.

The hemoglobin was 8.1 gm.; red cell count, 3,000,000; white cell count, 5,200. The serum bilirubin was 7.2 mg. per cent; serum albumin, 3.1 gm. per cent; serum globulin, 4.4 gm. per cent; cholesterol, 78 mg. per cent, with esters of 23 mg. per cent; the cephalin flocculation test was 3 plus. The serum calcium was 5.6 mg. per cent; serum phosphorus, 2.7 mg. per cent; alkaline phosphatase, 6.7 Bodansky units. The urine showed a negative Sulkowitch reaction.

The patient was placed on a high protein, low fat diet and was given daily intravenous injections of Intraheptol and several blood transfusions. On the fourth hospital day he felt extremely weak, developed convulsions and lost consciousness. At this time daily intramuscular injections of 200,000 U.S.P. units of vitamin D were begun. The patient succumbed three days later.

Postmortem examination revealed postnecrotic cirrhosis of the liver with esophageal varices. Examination of a piece of bone taken from the humerus showed thinning of the bony trabeculae, some of which were surrounded by well defined zones of osteoid.

Case 4. A 47 year old white female was admitted in September, 1949. Two months previously slight scleral icterus was noted. The patient was told she had a mild case of jaundice and was placed on a low salt diet and a few other medications. Increasing weakness, anorexia, a weight loss of 25 pounds and generalized pruritus set in and she was finally admitted to the hospital. There was no past history of abdominal pain, alcoholism or exposure to hepatotoxic substances.

Physical examination revealed a moderately icteric woman. No xanthomata of the skin were present. The liver was palpable five fingerbreadths and the spleen two fingerbreadths below the costal margin.

The hemoglobin was 75 per cent. The red cells were microcytic and hypochromic. The total white count was normal. The eosinophilic count ranged between 7 and 17 per cent. The urine showed the presence of bilirubin and 1:200 urobilinogen. Stercobilin and occult blood were present in the stool. The sedimentation

FIG. 5. *Case 4.* Patient with cholangiolitic cirrhosis and superimposed osteomalacia. Compression of thoracic and lumbar vertebral bodies.

rate was rapid, the icterus index was 40.5; the serum albumin and globulin were normal; cholesterol, 720 mg. per cent, with 170 mg. per cent esters; the alkaline phosphatase was 2.8 Bodansky units, and the cephalin flocculation test was 3 plus. The zinc turbidity was high; the prothrombin time was 82 per cent of normal. Intravenous and oral galactose tolerance tests were normal.

A gastrointestinal series and barium enema were unrevealing. Oral cholecystography failed to visualize the gall-bladder. Repeated liver biopsies showed moderate fatty infiltration, dilatation of small bile ducts in which many bile thrombi were present, and some focal round cell infiltration in the portal zones. This was interpreted as indicative of intrahepatic small bile duct obstruction. Because of the high serum cholesterol and other evidence of intrahepatic obstruction, a diagnosis of xanthomatous biliary cirrhosis was made.

The patient was placed on a high carbohydrate, high protein diet, with minimal fat and cholesterol content. She was given vitamins and a lipotropic agent. She continued at home on this therapeutic regimen, with slow improvement in appetite and a weight gain of 13 pounds. In November, 1950, xanthelasmata were noted on the eyelids.

In June, 1952, she was admitted again to the hospital with high fever and pyuria. On antibiotic therapy the fever subsided. Physical examination was unchanged from her previous admission, except for more marked jaundice and prominence of xanthelasmata. There was exquisite pain on pressure along the dorsal and lumbar spine, with limitation of motion. X-ray films of the spine showed compression of the vertebrae from the sixth dorsal to the second lumbar (figure 5). Several days after admission generalized ecchymoses developed, which disappeared promptly after intravenous vitamin K administration. The serum calcium was 9.2 mg. per cent; the phosphorus, 1.8 mg. per cent; the alkaline phosphatase, 10.8 Bodansky units. She was discharged with a diagnosis of xanthomatous biliary cirrhosis, compression fracture of the vertebrae due to demineralization, and pyelonephritis. At the time of discharge she was placed on testosterone (100 mg. weekly) and was advised to wear an orthopedic corset for the back pain.

At home she had frequent episodes of bleeding from the mucous membranes and ecchymoses of the skin. The prothrombin time was only 1.0 per cent of normal. Vitamin K given orally and parenterally usually controlled the hemorrhagic tendency. In December, 1952, edema of the legs and ascites developed.

The patient was admitted for the last time in February, 1953, with persistent vomiting and mental torpor. She was intensely jaundiced, with a brownish black pigmentation of the skin. Small scattered cutaneous xanthomata were noted. The liver was smaller than before, three fingerbreadths below the costal margin; the spleen was markedly enlarged. There were clubbing of the fingers, ascites, and edema of sacrum and extremities. Fetor hepaticus was present. The serum calcium was 9 mg. per cent; the serum phosphorus, 2.1 mg. per cent, and the alkaline phosphatase, 10 Bodansky units per 100 c.c. X-rays of the spine showed the findings previously noted and additional involvement of the upper thoracic vertebrae. It was now evident that this woman with long-standing obstructive icterus was suffering from osteomalacia secondary to prolonged biliary steatorrhea. The low serum phosphate certainly favored this diagnosis. The increase of the alkaline phosphatase of the serum, though possibly connected with the osteomalacia, was mainly due to the cholangiolitic liver cirrhosis. Large doses of vitamin D were given during the subsequent weeks, without noticeable improvement.

The remainder of the patient's course was slowly and progressively downward, with increasing evidence of liver failure. She died in April in coma, four months after admission.

A final biopsy of the liver revealed the presence of severe biliary cirrhosis.

Pathogenesis of Osteomalacia

Osteomalacia is a metabolic disease of bone. In this condition insufficient amounts of calcium and/or phosphorus are available. This prevents normal calcification of bone matrix and, in the long run, demineralization results.

Bone apparently is formed in two stages, the first being the laying down of an organic protein matrix by the cellular elements of bone, the osteoblasts. This matrix, called osteoid, consists largely of protein and contains considerable quantities of mucopolysaccharides in the form of highly acidic chondroitin sulfates. In the second stage of bone formation, newly formed osteoid is impregnated with calcium salts, mainly hydroxy-calcium phosphate. The crystal form of the bone salts closely resembles apatite, a hexagonal calcium phosphate which occurs in nature. Thus, nowadays the calcium phosphate of the bones is often designated as a hydroxyl-apatite with adsorbed carbonate, phosphate and fluoride.[1]

The exact mechanisms by which calcium and phosphorus are precipitated from the dissolved ions circulating in the extracellular fluids are not yet known. It is obvious, however, that calcium and phosphorus will precipitate only when the solubility product of these two ions is exceeded.

Irrespective of the mechanisms which bring about the precipitation of the calcium bone salts, as soon as the body is seriously depleted of either calcium or phosphorus the solubility product of the two ions cannot be exceeded. Then precipitation of calcium phosphate does not take place and newly formed osteoid does not calcify. Therefore, conditions which cause a negative calcium or phosphorus balance ultimately lead to a failure of the second stage of bone formation. If such a situation occurs in the growing child, then rickets develops.

In the adult, lack of absorption of calcium and phosphorus from the intestine leads to osteomalacia. Although in the adult the epiphyses are closed, there is still new formation of bone going on throughout the entire span of life. The adult bone is in a dynamic equilibrium. Continually a small amount of bone is resorbed and the same amount of bone is laid down in a process which proceeds slowly from day to day. In compact bone, this resorption and new formation take place along the cement lines of the haversian systems. In cancellous bone, it occurs at the edges of the trabeculae. In the adult, just as in the child, calcification of newly laid down osteoid suffers if the body stores of calcium have been depleted. The lamellae and trabeculae of preëxisting bone become surrounded by a broad layer of noncalcified bone matrix which histologically presents itself as eosinophilic-staining osteoid. The histologic finding of broad osteoid zones is a striking feature both in rickets and in osteomalacia.

After a state of calcium depletion has existed for a while a considerable proportion of the skeleton comes to consist of osteoid, and the bones are weakened for lack of mineral material. Bone pains appear, and roentgen

examination of the skeletal system reveals generalized demineralization and possibly pathologic fractures. Often roentgenograms disclose the presence of small fissures in the cortex of the long bones, consisting of proliferation of osteoid which remains uncalcified. These pseudo-fractures are designated as Looser's zones or Milkman's fractures. The serum calcium and phosphorus are low, reflecting the depletion of the calcium and phosphorus stores of the organism. For the same reason, practically no calcium is excreted in the urine. The qualitative test for calcium in the urine by the Sulkowitch reagent is negative, and careful balance studies on a Bauer-Aub diet reveal the excretion of only minute amounts of calcium in the urine. As the skeleton weakens the bones are submitted to greater stress, which gives rise to an increase in osteoblastic activity. This in turn causes an increase in the serum alkaline phosphatase. It should be noted, however, that early in osteomalacia, before marked weakening of the skeleton has occurred, the alkaline phosphatase may be normal, despite altered values for calcium and phosphorus of the serum. In this way the general clinical and biochemical picture in rickets and osteomalacia develops.

The finding of any abnormally low serum calcium and/or inorganic phosphorus is an essential feature of rickets and osteomalacia, without which the diagnosis cannot be made.

The level of serum calcium and phosphorus is carefully regulated by the parathyroid glands. As there is no pituitary trophic hormone controlling their activity, these glands respond directly and sensitively to changes in the level of serum calcium. When the level of serum calcium falls, an increased secretion of parathormone occurs. Current opinion holds that parathormone causes bone resorption by causing dissolution of organic bone matrix. As the osteoid matrix dissolves, the calcium with which it is impregnated is freed to enter the interstitial tissues of the body. Carnes [2] has shown that in rachitic rats with the usual abundance of osteoid, parathormone causes a rapid resorption of this substance. Also, it is known that following a single injection of parathormone there is a large increase in circulating serum mucopolysaccharides, substances of which osteoid contains large quantities.[3]

In addition, parathormone reduces the renal tubular reabsorption of phosphate, causing an increased loss of this ion in the urine.[4] Hyperphosphaturia leads to hypophosphatemia. This permits more calcium to exist in the ionic state in the serum before the solubility product of calcium and phosphorus is exceeded. Thus, as a side action to the renal action of parathormone on the phosphate excretion by the kidney, the serum calcium level rises.

Therefore, in osteomalacia with hypocalcemia the parathyroids secrete additional parathormone. If this compensatory response is complete, the serum calcium returns to normal and the serum phosphorus is depressed by the excess amount of phosphates excreted under influence of the parathyroid hormone. Case 4 illustrates this pattern of normal serum calcium together

with low serum phosphorus in osteomalacia. At times, however, there is only a partial compensatory response of the parathyroids. Then serum calcium levels tend to return to normal, but remain subnormal, and serum phosphorus is low due to the renal action of parathormone. The pattern in such a case is a slightly diminished serum calcium and moderately low phosphorus, as seen in case 1. Rarely, the parathyroids fail totally, and the serum calcium falls to very low levels while the phosphorus remains normal. In such cases tetany may result. Such findings were present in case 3. Thus, depending on secondary reactions of the parathyroid glands, the serum in osteomalacia may show normal calcium with low phosphorus, slightly low calcium with low phosphorus, or low calcium with normal phosphorus. The elevated alkaline phosphatase which is part of the biochemical picture has already been mentioned.

That the parathyroids may respond to calcium depletion in osteomalacia is supported by the observation of Erdheim, who in 1907 discovered hyperplasia of these glands in three cases of osteomalacia at postmortem examination.[5] Since then this observation has been repeated, and hyperplastic parathyroid glands have been found frequently in humans and in experimental animals suffering from osteomalacia.[6, 7, 8]

Etiology of Osteomalacia

A negative calcium balance leading to osteomalacia may come about in various ways. The most obvious cause is evidently a simple lack of vitamin D. This vitamin is the chief agent controlling absorption of calcium from the intestine; and although the fundamental mechanisms involved in this control are unknown, it has been amply demonstrated that in humans and in animals depleted of vitamin D, little if any calcium is absorbed. Animal experiments seem to indicate that in avitaminosis D the calcium absorption from the distal part of the ileum and the colon is much more impaired than the calcium absorption from the proximal two third parts of the ileum.[9] Thus, in this condition most of the ingested calcium is lost in the feces. In certain regions of the world environmental conditions, that is, lack of exposure to sunshine combined with a lack of vitamin D in the diet, may lead to an impressive incidence of osteomalacia in the population. In North China, for instance, the food is practically devoid of animal fat (the main source of vitamin D).[10, 11] The poorer women cannot sufficiently expose themselves to sunlight because they are tied up in their homes by overwhelming domestic duties. Frequent pregnancies and—still more important—prolonged breast feeding result in considerable losses of vitamin D and calcium from the maternal organism. All this explains why osteomalacia is frequently seen in the adult women in North China. Contrariwise, the abundance of sunshine in South China and other tropical countries prevents the development of osteomalacia. Only the well-to-do Mohammedan married women who were obliged to stay indoors day and night in the seraglio

developed osteomalacia, even in the tropics. The studies of Maxwell in North China did much to prove that osteomalacia resulted from avitaminosis D, and that it was identical with the rickets of childhood.[12] He observed that in China late rickets and osteomalacia were more common than infantile rickets. The rarity of the latter form of avitaminosis D must be correlated with the fact that infants and young children are left to play in the open courtyards for long periods during the day, thus providing themselves with sufficient vitamin D to prevent rickets, despite a grossly deficient diet.

Low calcium intake per se is not a major factor in the pathogenesis of osteomalacia. Maxwell and collaborators clearly demonstrated that the condition of osteomalacic patients does not improve under the influence of increased calcium intake without addition of vitamin D. Nevertheless, it seems highly probable that avitaminosis D may be aggravated by an insufficient calcium intake, and that the best therapeutic results are obtained when vitamin D and calcium salts are administered simultaneously.

In the United States such dietary and environmental conditions as prevail in North China do not exist, and in this part of the world osteomalacia is hardly ever due to inadequate intake of vitamin D.[11] Nevertheless, even in New York osteomalacia still occurs occasionally, usually in conditions which interfere with the intestinal absorption of fats, fat-soluble vitamins, calcium and phosphorus. Steatorrhea, occurring in the sprue syndrome or in the course of long-standing biliary obstruction, or in a case of obstruction of the pancreatic ducts, is the most common cause. For when fat is poorly absorbed it carries with it into the stool most of the dietary fat-soluble substances, and in this way most of the ingested vitamin D is lost. For completeness' sake it should be added that the same holds true for other fat-soluble vitamins A and K. At the same time the non-absorbed fatty acids combine with the calcium present in the intestine, and large quantities of calcium are eliminated in the form of insoluble calcium soaps. In cases where these losses of both vitamin D and calcium are prolonged over a considerable period of time, osteomalacia results.

It appears from a carefully controlled metabolic study that in steatorrhea the hypovitaminosis D is the most important factor causing a negative calcium balance. Bauer and Marble,[13] studying the calcium balance in a case of pancreatic steatorrhea, showed that the absorption of calcium can be brought to normal by the administration of large amounts of vitamin D, despite the fact that the diet was unchanged and fatty stools persisted. The calcium content of the diet, therefore, plays only a minor rôle in the causation of osteomalacia, irrespective of whether the disease is due to lack of sunshine and absence of vitamin D in the food or whether the disease occurs in the course of prolonged fatty diarrhea.

A small group of cases of osteomalacia is seen in association with the rare syndrome of renal tubular acidosis. In this renal disease the inability of the kidney tubules to reabsorb basic radicals causes considerable loss of

the fixed base of the body, including large quantities of calcium in the urine. A negative calcium balance ensues, beginning the biochemical sequence which ends in clinical osteomalacia. The other, even rarer syndrome is idiopathic hypercalciuria. In this disease there is a marked increase in the urinary excretion of calcium, despite the presence of normal serum calcium levels. Not all cases lead to osteomalacia, but the possibility of depleting the body of calcium exists, and several cases associated with osteomalacia have been reported.[13]

The cases included in this report are all examples of osteomalacia which developed during the course of prolonged steatorrhea. Case 1 is a clear-cut sprue syndrome showing advanced osteomalacia with typical clinical and biochemical findings. Bone pain and diarrhea were the presenting complaints. X-rays revealed marked generalized demineralization of the skeleton with symmetrical fractures of the pubic bones. Both the serum calcium and phosphorus were low, and the alkaline phosphatase was elevated. Only a small amount of calcium was excreted in the urine. Rapid improvement of the condition of the skeleton, a rise in the serum phosphorus, and increased urinary calcium excretion followed the parenteral administration of vitamin D. Quantitative studies of the fecal fat content proved the existence of steatorrhea, which was the cause of the osteomalacia.

Some question exists in this case as to the etiology of the steatorrhea. This could have been simply another example of so-called idiopathic steatorrhea, the celiac disease of adults. However, the patient had unequivocal evidence of scleroderma involving the skin, and this suggests the possibility that sclerodermatous changes in the small intestine were the cause of the steatorrhea. Extensive involvement of the intestine has been reported frequently in scleroderma.[14, 15] Fatty diarrhea has also been observed in scleroderma by other clinicians.[16] Adlersberg has studied cases of scleroderma with roentgen evidence of involvement of the small intestine, and has demonstrated the presence of steatorrhea in such cases.[17]

Cases 2 and 4 are examples of prolonged biliary steatorrhea which gave rise to osteomalacia. In case 2 there was obstruction to the large bile passages producing a true biliary cirrhosis. In case 4, blockage of the finer biliary radicles was due to the development of so-called cholangiolitic biliary cirrhosis (primary biliary cirrhosis). In both cases bile salts were not available for the emulsification and absorption of fats, and in both cases osteomalacia developed. In case 2 the calcium and phosphorus values do not confirm the diagnosis of osteomalacia. However, there is only one series of determinations available, and the improvement on treatment with vitamin D and ultraviolet light was impressive. In case 4 it is of interest that when the patient first complained of bone pain, and demineralization of the skeleton was visualized roentgenologically, androgens were given therapeutically and, as might have been expected, no improvement resulted. In such cases of prolonged biliary obstruction with steatorrhea, at the first

suspicion of disease of the bone, determinations of serum calcium and phosphorus and of urinary calcium excretion are in order. When the result of these analyses confirms the diagnosis of osteomalacia, then the proper treatment consists of parenteral administration of vitamin D and ultraviolet irradiation.

Case 4 also illustrates that fat-soluble vitamins other than vitamin D are lost in the feces in fatty diarrhea. On several occasions this patient showed marked hemorrhagic skin manifestations which were due to abnormally elevated prothrombin time. Parenteral administration of vitamin K corrected the defect each time.

Ahrens et al.[18] studied 22 cases of primary biliary cirrhosis and were able to demonstrate significant steatorrhea in 21 cases. Twelve patients showed generalized demineralization of the skeleton and seven complained of bone pain. Serum calcium and phosphorus values were not available, but five of six cases treated with vitamin D experienced relief of pain. The authors felt that osteomalacia was the main cause of the decalcification, but that there was also a certain amount of superimposed osteoporosis. In their study, circulating estrogen levels were assumed to be low as judged by the vaginal smear technic, and it was thought that some osteoporosis resulted from this estrogen deficiency.[18]

Occasionally a widespread granulomatous jejuno-ileitis gives rise to steatorrhea; and less extensive disease, if associated with resections or short-circuiting of portions of the small intestine, may do the same. Albright has reported a case of this type in which there was evidence of a deficiency of vitamins D, K, and A. Osteomalacia was present.[19] Case 3, in which an ileostomy had been present for several years, is of a similar nature. While the long-standing ileostomy was obviously the major factor causing steatorrhea, hepatic disease was present during life and a toxic nodular cirrhosis was discovered at autopsy. It is possible that this essentially parenchymal disease of the liver also contributed to the patient's steatorrhea and consequently to his osteomalacia, since Gross et al. have shown that steatorrhea is a not uncommon finding in parenchymal disease of the liver. It is frequently present in ordinary Laennec's cirrhosis.[20]

Summary

Four cases of osteomalacia observed in New York City are reported. All cases suffered from fatty diarrhea. In two cases the steatorrhea was due to chronic jaundice, in one case to scleroderma, and in one case to long-standing ileostomy.

The pathogenesis of osteomalacia occurring in cases of chronic steatorrhea is discussed, and the importance of the loss of fat-soluble vitamin D in the fatty stools is emphasized.

Treatment should consist of parenteral vitamin D administration and radiation with ultraviolet light.

BIBLIOGRAPHY

1. Gutman, A. B.: Current theories of bone formation, Bull. Hosp. Joint Dis. **12**: 74, 1951.
2. Carnes, W. H.: The demonstration of an effect of parathyroid extract on bone matrix, Am. J. Path. **26**: 736, 1950 (Scientific Proceedings).
3. Engel, M. B.: Mobilization of mucoprotein by parathyroid extract, Arch. Path. **53**: 339, 1952.
4. Snapper, I.: Parathyroid hormone and mineral metabolism, Bull. New York Acad. Med. **29**: 612, 1953.
5. Erdheim, J.: Ueber Epithelkörperbefunde bei Osteomalacie, Sitzungsb. d. Akad. d. Wissensch., Math.-naturw. Kl. Wien **116**: 311, 1907.
6. Gunn, F. D., and Nadler, W. H.: Osteomalacia. Necropsy observations in a man, Arch. Int. Med. **54**: 145, 1934.
7. Liu, S. H., Ch'in, K. Y., Chu, H. I., and Pai, H. C.: Osteomalacia. Clinical, metabolic and pathological studies of a case with parathyroid hyperplasia and right-sided cardiac hypertrophy from thoracic deformity and vitamin B_1 deficiency, Chinese M. J. **58**: 141, 1940.
8. Luce, E. M.: The size of the pituitary of rats and the effect of a dietary deficiency of calcium, J. Path. and Bact. **26**: 200, 1923.
9. Harrison, H. E., and Harrison, H. C.: The uptake of radiocalcium by the skeleton, J. Biol. Chem. **185**: 857, 1950.
10. Snapper, I.: Medical clinics on bone diseases, 1949, Interscience Publishers, New York.
11. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr., and Roos, A.: Osteomalacia and late rickets, Medicine **25**: 399, 1946.
12. Maxwell, J. P.: Osteomalacia and fetal rickets, Proc. Roy. Soc. Med. **23**: 19, 1930. Further studies in adult rickets (osteomalacia) and fetal rickets, Proc. Roy. Soc. Med. **28**: 265, 1935.
    Maxwell, J. P., Hu, C. H., and Turnbull, H. M.: Foetal rickets, J. Path. and Bact. **35**: 419, 1932.
13. Bauer, W., and Marble, A.: Studies on mode of action of irradiated ergosterol, its effect on calcium and phosphorus metabolism of individuals with calcium deficiency diseases, J. Clin. Investigation **11**: 21, 1932.
14. Bevans, M.: Pathology of scleroderma with special reference to the changes in the gastrointestinal tract, Am. J. Path. **21**: 25, 1945.
15. Robles Gil, J.: Clinical study of small bowel visceral lesions and endocrine disturbances in eight cases of diffuse scleroderma, Ann. Int. Med. **34**: 862, 1951.
16. Deenstra, H., and Jansen, L. H.: Longafwijkingen Bij Sclerodermie, Nederl. tijdschr. v. geneesk. **96**: 3073, 1952.
17. Adlersberg, D.: Personal communication.
18. Ahrens, E. H., Jr., Payne, M. A., Kunkel, H. G., Eisenmenger, W. J., and Blondheim, S. H.: Primary biliary cirrhosis, Medicine **29**: 299, 1950.
19. Albright, F., and Steward, J. D.: Hypovitaminosis of all fat-soluble vitamins due to steatorrhea; report of case, New England J. Med. **223**: 239, 1940.
20. Gross, J. B., Comfort, M. W., Wollaeger, E. E., and Power, M. H.: Total solids, fat and nitrogen in feces: study of patients with primary parenchymatous hepatic disease, Gastroenterology **16**: 140, 1950.

THE RELATION OF PHYSICAL ACTIVITY AND OCCUPATION TO CORONARY ARTERY HEART DISEASE*

By Joseph G. Benton, Ph.D., M.D., and Howard A. Rusk, M.D., F.A.C.P., *New York, N. Y.*

Introduction

It has been suggested that there has been an increased incidence of coronary artery heart disease in recent years. This disease of modern civilization has assumed prominence during a period in which heavy labor is less common and length of work hours has decreased; while other pressures have increased. Constitutional factors are important in coronary artery heart disease, but there is also evidence of variation of its incidence with environment. In addition, its relationship to physical effort is highly controversial, with, in many instances, significant medicolegal connotations.

Special interest in the general area of physical activity and coronary artery heart disease originally stemmed from our experience with approximately 1,000 patients in the Department of Physical Medicine and Rehabilitation of the New York University-Bellevue Medical Center whose hemiplegia was a complication of underlying systemic cardiovascular disease. These patients passed through a graduated rehabilitation program of retraining, including, among other procedures, activities of daily living and ambulation ranging from level walking to stair climbing of varying intensity. While complete follow-up data for these patients are presently not available, only rarely did their cardiovascular status deteriorate clinically while under observation. In this connection, it should be emphasized that rehabilitation was not considered feasible in any patient in whose case: (1) there had been such cerebral damage as to preclude adequate mentation to allow for recall of retraining technics, (2) the malignant phase of arteriolonephrosclerosis had supervened, and (3) intractable congestive heart failure or coronary insufficiency was present. Indeed, these were considered contraindications for patient selection.

Review of Literature

Review of the literature indicates that there are divergent opinions concerning the relationship of effort or stress to coronary thrombosis. One group believes that coronary thrombosis almost invariably occurs in the

* Presented as a Morning Lecture at the Thirty-fifth Annual Session of the American College of Physicians, Chicago, Illinois, April 7, 1954.

From the Department of Physical Medicine and Rehabilitation and the Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York, N. Y.

absence of effort, usually at night, and often in the early morning hours, when the blood pressure is low and the coronary blood flow diminished. Some maintain that angina pectoris is almost always precipitated by stress, either physical or psychologic, and that these are related to coronary insufficiency in roughly 50 per cent of cases but are coincidental in the pathogenesis of coronary thrombosis.[1, 2, 3, 4, 5] Others believe that there is good evidence that sudden, exceptionally heavy physical exertion may be followed by coronary occlusion.[6, 7, 8] In addition, there are those who believe that acute psychologic disturbances may have a direct bearing on coronary occlusion.[9, 10] All are agreed, however, that preëxisting intrinsic coronary artery disease must be present.

With reference to psychosomatic factors in the pathogenesis of this syndrome, it is of interest to note that there have been described [11] increased capillary permeability and hemorrhage, hemoconcentration and hypertension or hypotension (depending on the intensity of the stress) during the alarm reaction "of the general adaptation syndrome." In addition, it has also been demonstrated that significant changes in hemodynamics and electrocardiographic patterns occur during psychiatric interviews relating to stressful life situations.[12] Exercise and emotional stress have also been shown to cause not only changes in blood pressure but also an increase in blood viscosity and hematocrit, and a decrease in sedimentation rate and coagulation and prothrombin times.[13] It would appear, therefore, that there is objective evidence of the influence of physical and emotional factors on the vascular tone and the clotting mechanisms of the blood, and that the central nervous and endocrine systems may be involved.

The suggested increase in coronary artery heart disease is not due simply to an increase in coronary artery atheromata. Other conditions are necessary, and the complex of atheroma, thrombosis and the capacity of the heart to deal with these in relation to the demands made upon it is an important consideration. Some information relative to this has appeared in the American literature, but the most extensive surveys in this connection have been made recently by the Social Medicine Research Unit of the Medical Research Council of Great Britain under the direction of Dr. J. N. Morris.[14, 15, 16, 17] It was hoped that these studies would afford knowledge of coronary artery heart disease as a public health problem, and also that possible social factors which may be favorable or unfavorable to its incidence might be delineated.

It is the purpose of this paper to present data derived by means of standard epidemiologic technics from both American and British literature which may have bearing on the problem of physical activity and occupation and coronary artery heart disease.

The occurrence of coronary artery heart disease in certain groups of weekly paid employees of the London Transport Executive during 1949 and 1950 was carefully studied in approximately 31,000 men aged 35 to 64. The experience of drivers and conductors of the "red" buses (double deck),

drivers and conductors of trains and trolley buses, and the motormen and guards on the underground railways was observed. Analysis of the data suggested that coronary artery heart disease behaves differently in the drivers (sedentary) and in the conductors (active). Angina pectoris was relatively more common among the conductors, rapidly fatal coronary thrombosis among the drivers. Thirteen per cent of the first episodes among the drivers took the form of angina—or were so diagnosed—compared with 39 per cent in the conductors. Contrariwise, the "immediate" deaths accounted for 31 per cent in the drivers (25 "immediate" deaths in 80 cases), as against 19 per cent in the conductors. The conductors therefore had less lethal coronary artery heart disease than the drivers, and the disease seemed to be appearing in them at a later age. What disease the conductors had was less severe, with a smaller early case fatality as well as a lower incidence, and therefore a substantially lower early mortality rate. On the other hand, the conductors manifested more of the benign type of disease, in the form of angina pectoris, than the drivers. These observations were judged reliable since there was a triple check on the diagnoses—the men's own general practitioners, medical officers of the London Transport Executive and, in addition, corroboration in over 90 per cent of the cases through documented confirmation by a specialist and/or a hospital. Most significant is that this was an epidemiologic study of the experience of different occupational *groups*. The population consists of men from the same part of the country, served by the same health and welfare services, and living in broadly similar social circumstances during the same period of time. Conditions of sickness absence and benefit are similar throughout for the population studied.

The differences in figures between drivers and conductors are considered significant ($p. = < .001$) when statistically analyzed. Therefore, they would appear not to be due to faulty data or small numbers. Possibilities for the observed variations: (1) There may be differences in constitution and early experience of the conductors and drivers, another expression of which is that the men select for themselves their very different jobs. (2) While there may be mental strains in both driving and conducting, these may be of different kinds, and the difference may be a factor in the higher incidence and mortality among the drivers. (3) The greater physical activity of "conducting" on the double decker vehicles may be a cause of the lower incidence and mortality in the conductors.

The latter seemed the most likely explanation, and the hypothesis was tested by making a similar two-year study of the mortality and morbidity statistics referable to coronary artery heart disease in 110,000 men 35 to 59 years of age who were Postal workers and Civil servants and whose work involved three major categories of physical activity.

The results show that the total incidence of coronary artery heart disease is lower in postmen (active) than in the sedentary grades. Their case fatality is also lower: a third in the postmen (57 of 171), compared with

almost a half in telephonists, executives and clerks (70 of 143). Again, as with the transport workers the early mortality of the physically active group (0.6 per 1,000) is substantially less than that of the physically inactive (1.2 per 1,000). On the other hand, the incidence of angina is higher in the postmen than in the sedentary workers (0.7 per 1,000 against 0.5 per 1,000). The postal grades which are "intermediate" with respect to physical activity show total incidence and early mortality rates that lie, on the whole, between those of the postmen and the sedentary grades.

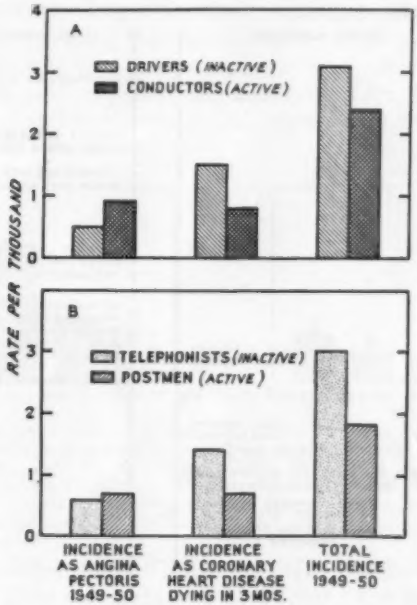


FIG. 1. First clinical episodes of coronary heart disease in 1949–52: A, drivers and male conductors, aged 35–64, of Central London Buses; B, G.P.O. male telephonists and postmen, aged 35–59. (From J. N. Morris et al.—published by permission.)

The experience of the postal workers and the civil servants may therefore be said to resemble that of the transport workers: the physically active group (the postmen) have less coronary artery heart disease, and what disease they do have is less severe (figure 1). It would thus appear that the data strongly suggest that physical activity at work is important in relation to the coronary artery heart disease of middle-aged men.

Further confirmation of this premise was afforded by an analysis of the mortality due to coronary artery heart disease related to strenuousness of work in the total male working population aged 45 to 54 in England and Wales in 1930–1932. Briefly, the coronary mortality of the groups doing

physically heavy work is less than half that of the light groups (figure 2). This figure plots the mortality rates of occupation groups and shows almost no overlap of heavy and light groups. If there is a major psychologic factor operating to produce the mortality gradient already noted, the scatter of this chart suggests that it is so intimately associated with the physical factor as not to be readily distinguishable from it. The early observations of 1930–1932 were corroborated by analyses of records of men aged 45 to 74 dying of coronary artery heart disease in London and home counties

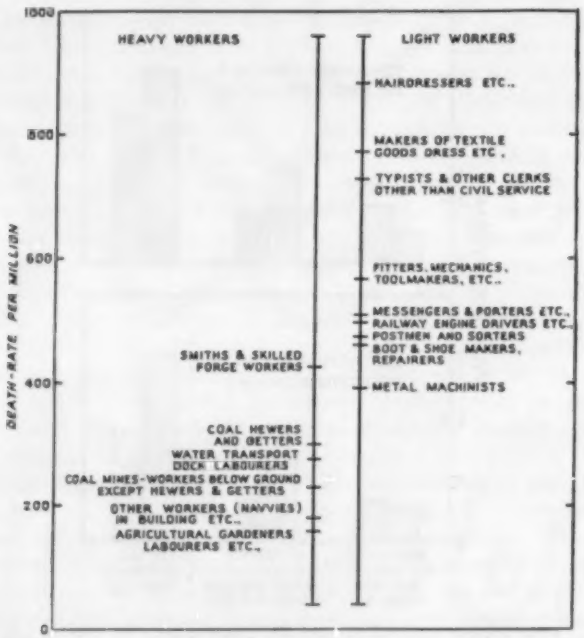


FIG. 2. Mortality from coronary heart disease in heavy and light workers, men aged 45–64, in England and Wales in 1930–32. Rates for occupation groups in social classes iii, iv, and v having 10 or more deaths per year. (From J. N. Morris et al.—published by permission.)

in March, 1952. This would tend to obviate the technical question of possible variations in diagnoses.

In this country, while as complete studies are not available, a survey of death rates by occupation performed in the pre-depression era (based on data of the United States Census of 1930) revealed that farmers and agricultural workers, as a group, had the lowest mortality rate, followed next in incidence by the executive socio-economic group. Confirmation of this for the executive group was afforded by a report of the Joint Com-

mittee on Mortality presented in the 1949 Transactions of the Society of Actuaries, which indicated that the executive group (those carrying large amount life insurance policies) did not have an increased mortality as compared to individuals insured for small amounts. Such evidence should be borne in mind in evaluating a statement made in a recent *Fortune* magazine article—"The number of executives nipped in mid-career seems to be rising, and the frequency with which 'heart failure' is cited gives this the status of an occupational disease"—as well as when reading obituaries of prominent industrial figures in the morning newspapers.

Of special interest, and in some respects contradictory to the previous general conclusions regarding the relationship of type of work and coronary artery heart disease, are data concerning physicians. A study [18] was made of over 6,000 male medical practitioner members of the Medical Sickness, Annuity and Life Assurance Society, Ltd., aged 35 to 64, who held "im-

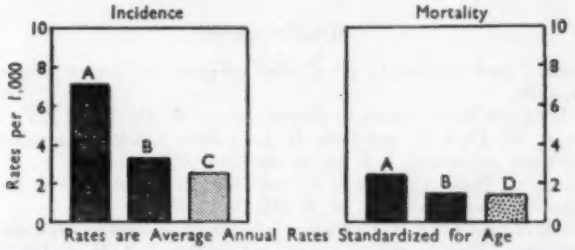


FIG. 3. Coronary heart disease in medical practitioners and in others. Men aged 40–59, inclusive. A = General practitioners (Category 1), 1947–50. B = Other doctors (Categories 2 + 3 + 4), 1947–50. C = Miscellaneous non-medical group, 1949–50. D = England and Wales, Civilian Population, 1950 (provisional). A and B held Medical Sickness, Annuity and Life Assurance Society Immediate Benefit Policies. (From J. N. Morris et al.—published by permission.)

mediate" non-cancellable sickness insurance. The incidence of first attacks of coronary artery heart disease in 1947–1950 was twice as high among the full-time general practitioners aged 40 to 64 as in full-time consultants or specialists, and public health officials. When "G-P-specialists" were added to the full-time general practitioners, the incidence in the composite group was 1.8 times that in the remainder. Finally, the incidence of coronary artery disease in a large group of non-medical men of comparable age in the civil services, the professions and in industry was well below that of the full-time general practitioners, and resembled that of the other physicians (figure 3). A comparison with the provisional mortality rates from coronary disease among the males of comparable age of England and Wales in 1950 gave similar results. Comparable data have been presented in studies done in this country in 1947–1948.[19, 20] It is possible that the well-known day-to-day stress, other than physical, under which the average general practitioner operates may be a causative factor for the increased

mortality in this group. Such factors, not the least of which may be psychologic, would admittedly be difficult to quantitate.

Reasons for these significant facts are not immediately apparent, but there is little doubt that further studies relating to coronary artery heart disease and physical and psychologic factors, the effect of physical activity on coronary circulation, other occupational and social factors, nutritional factors (including obesity) and constitutional factors are clearly indicated.

Summary

In summary, (1) it would appear that except for the general medical practitioner the old adage, "Hard work never killed anybody," seems to have some objective basis in fact; and (2) physical activity of the type usually undertaken in rehabilitation programs is not detrimental to the properly selected patient.

BIBLIOGRAPHY

1. Parkinson, J., and Bedford, D. E.: Cardiac infarction and coronary thrombosis, Lancet **1**: 4, 1928.
2. Luten, D.: Contributory factors in coronary occlusion, Am. Heart J. **7**: 36, 1931.
3. Master, A. M., Dack, S., and Jaffe, H. J.: Factors and events associated with onset of coronary thrombosis, J. A. M. A. **109**: 546, 1937.
4. Master, A. M., Dack, S., Field, L. E., and Horn, H.: The diagnosis and treatment of coronary artery disease, J. A. M. A. **141**: 887, 1949.
5. Master, A. M., and Jaffe, H. J.: Factors in the onset of coronary occlusion and coronary insufficiency, effort, occupation, trauma and emotion, J. A. M. A. **148**: 794, 1952.
6. Fitzhugh, G., and Hamilton, B. E.: Coronary occlusion and fatal angina pectoris. Study of the immediate causes and their prevention, J. A. M. A. **100**: 475, 1933.
7. Boas, E. P.: Angina pectoris and cardiac infarction from trauma or unusual effort, J. A. M. A. **112**: 1887, 1939.
8. Boas, E. P.: Cardiac infarction induced by unusual effort, J. Mt. Sinai Hosp. **7**: 307, 1941.
9. Arlow, J. A.: Identification mechanisms in coronary occlusions, Psychosom. Med. **7**: 195, 1945.
10. Weiss, E., and English, O. S.: Psychosomatic medicine, 1954, W. B. Saunders Company, Philadelphia.
11. Selye, H., and Fortier, C.: Adaptation reactions to stress, *in* Proceedings of the Association for Research in Nervous and Mental Disease, 1950, Williams and Wilkins Co., Baltimore, Maryland, p. 3.
12. Stevenson, I., and Duncan, C. H.: Alterations in cardiac function and circulatory efficiency during periods of life stress as shown by changes in the rate, rhythm, electrocardiographic pattern and output of the heart in those with cardiovascular disease, *in* Life Stress and Bodily Disease; Proceedings of the Association for Research in Nervous and Mental Diseases, 1950, The Williams and Wilkins Company, Baltimore, Maryland, p. 799.
13. Schneider, R. A.: Relation of stress to clotting time and other biophysical alterations, *in* Life Stress and Bodily Disease, Proceedings of the Association for Research in Nervous and Mental Disease, 1950, Williams and Wilkins Company, Baltimore, Maryland, p. 818.
14. Morris, J. N.: Recent history of coronary disease, Lancet **1**: 1–7; 69–73, 1951.

15. Morris, J. N., and Heady, J. A.: Mortality in relation to the physical activity of work, Brit. J. Indust. Med. **10**: 245 (Oct.) 1953.
16. Morris, J. N., Heady, J. A., Raffel, P. A., Roberts, C. G., and Parks, J. W.: Coronary heart-disease and physical activity of work, Lancet **2**: 1053 (Nov. 21) 1953.
17. Morris, J. N., Heady, J. A., Raffel, P. A., Roberts, C. G., and Parks, J. W.: Coronary heart-disease and physical activity of work, Lancet **2**: 1111 (Nov. 28) 1953.
18. Morris, J. N., Heady, J. A., and Barley, R. G.: Coronary heart disease in medical practitioners, Brit. M. J. **1**: 503, 1952.
19. Dublin, L. I., and Spiegelman, M.: The longevity and mortality of American physicians 1938–1942. A preliminary report, J. A. M. A. **134**: 1211 (Aug. 9) 1947.
20. Dublin, L. I., and Spiegelman, M.: Mortality of medical specialists 1938–1942, J. A. M. A. **137**: 1519 (Aug. 21) 1948.

THE ELECTROCARDIOGRAM IN THE EXAMINATION OF THE INDUSTRIAL WORKER *

By J. Richard Durham, M.D., F.A.C.P., and Lemuel C. McGee, M.D., F.A.C.P., *Wilmington, Delaware*

The increasing use of the electrocardiograph in industry has prompted us to attempt an evaluation of its worth. Primarily, such a diagnostic instrument used in preplacement and periodic industrial examinations can benefit the individual employee by (1) uncovering disease in an early and possibly remediable stage; (2) identifying benign or inconsequential abnormalities which, without correct diagnosis, may lead to apprehension and anxiety as well as to erroneous employment restrictions, and (3) aiding placement of the worker in a job suited to his physical limitations if significant disability actually exists. Secondarily, there is value in a "base line" electrocardiogram for comparison with later records in the recognition of coronary artery disease when such develops. Furthermore, the large number of serial tracings, taken over many years on individuals in good health or in subclinical ambulatory disease states, add to our understanding of the place of the electrocardiogram in medical diagnosis and prognosis.

Material and Method

We have reviewed electrocardiograms taken on employees of the Hercules Powder Company since 1936. In the beginning tracings were taken on workers, almost all male, who were employed in potentially hazardous occupations. The three standard limb leads only were used between 1936 and 1939. In 1940 Lead IVF (electrode in the fourth intercostal space with its center on a line midway between the left margin of the sternum and the left midclavicular line) was added and records were taken periodically in the plants concerned on all employees over 40 years of age, in addition to those individuals who had potentially hazardous work. Hence, a survey of workers in both "white collar" and labor activities was permitted. Beginning in 1942, multiple chest leads were taken in many instances. Electrocardiographic interpretations were made on the basis of presently accepted criteria.[1] Clinical examinations, including laboratory work and chest x-rays where indicated, were available to aid in the correlation of findings from medical examinations with the tracings. From 1936 to 1952, approximately 37,000 tracings were obtained on 7,400 individuals ranging in age from 18 to 75 years. Minor deviations, such as changes in T_3, slurring QRS complexes of normal measurement, low voltage, left and right axis deviations, premature beats, and variability in the

* Received for publication January 8, 1954.

TABLE 1

Summary of Electrocardiographic Abnormalities

	Number	Number Working	Average Elapsed Time, of Those Working, Since Diagnosis	Comment
Left heart strain	66	41	5.3 years	
Myocardial infarction with recovery	51	22	5.2 years	14 subsequent deaths
Right bundle branch block	20	10	4.5 years	No clinical heart disease
S-type block	10	7	5.6 years	No clinical heart disease
Left bundle branch block	14	5	5.0 years	10 with clinical heart disease
Auricular fibrillation	20	19	6.0 years	One received disability pension

amplitude of T waves from year to year, are not considered as abnormalities for the purpose of this report (table 1). We attach no significance to the incidence of the findings in relation to the number of employees involved, since the records from some plants were sent to the central medical office on the basis of selection for consultation; in other plants, local cardiologists were used for this purpose and the authors did not see such records. Furthermore, there were, no doubt, instances of acute or suddenly manifest heart disease which were not brought to our attention, especially if the patient changed jobs following his illness.

STRAIN PATTERN

There were 66 cases of so-called "left heart strain" [2] discovered on serial tracings. The gradual development of left heart strain was indicated first by a lowering of T_1 amplitude and with T_3 becoming less inverted or iso-electric. This was followed by further lowering of T_1 through the iso-electric line to inversion, accompanied by increasing height of T_3. At some point in the evolution of this pattern—usually when T_3 became greater than T_1—strain was diagnosed. Where no previous tracings were available for comparison, a more typical pattern was necessary for reaching this conclusion. We were loath to diagnose strain in the presence of left axis deviation without erection of T_3.

At the time of the review there were 41 men in this group who had performed satisfactorily in moderately heavy to light work for an average of 5.3 years after recognition of a definite strain pattern (figures 1 and 2). Two showed a persistently increasing strain pattern for 11 years, one for 12 years, and one for 10 years. In none could one say that this electrocardiographic pattern per se resulted in disability or limitation of work. However, five such workers required a change in jobs because of symptoms resulting from hypertensive disease, after an average of three years with the strain pattern. There was no correlation between the prominence of the strain pattern and the height of the blood pressure. Typically, a

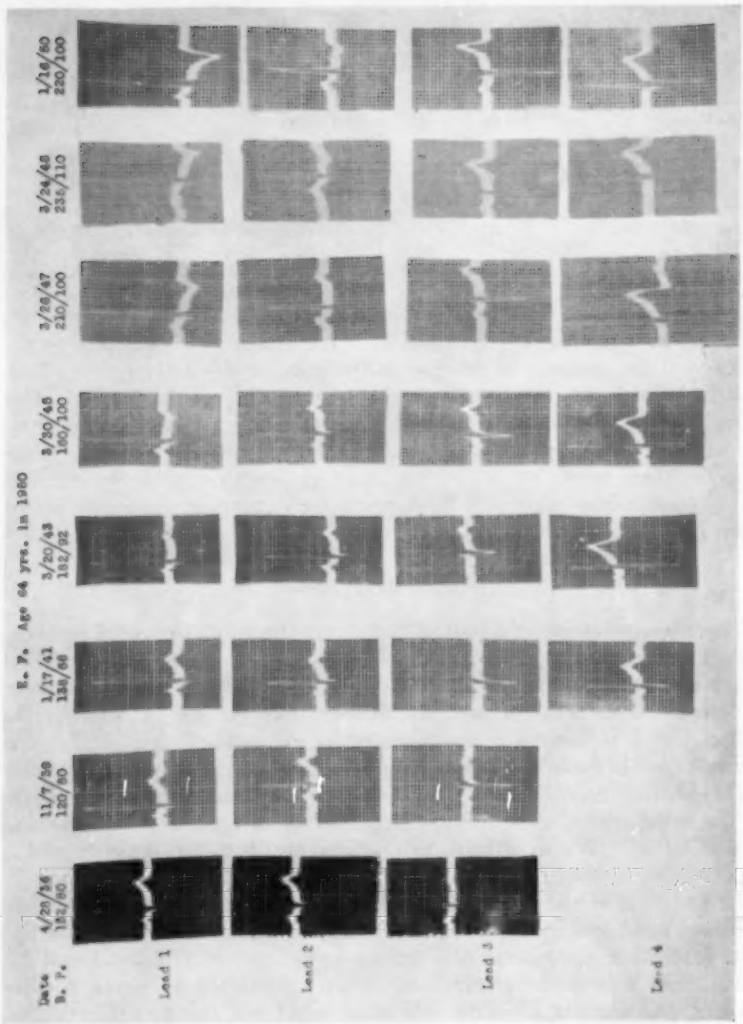


FIG. 1. Progressive hypertensive disease to retirement at age 65. Worked as chemist. No complaints.

blood pressure elevation (above 150/90 mm. of mercury) preceded for some years the onset of electrocardiographic change. Occasionally, persistent hypertension was present for years with no strain pattern developing (figure 4), and rarely a fixed strain pattern was seen in a worker with normotension.

Three instances of strain pattern, developing suddenly in normotensive individuals with normal heart size by x-ray, appeared to result from small anterior myocardial infarcts not transmural in extent. This diagnosis was

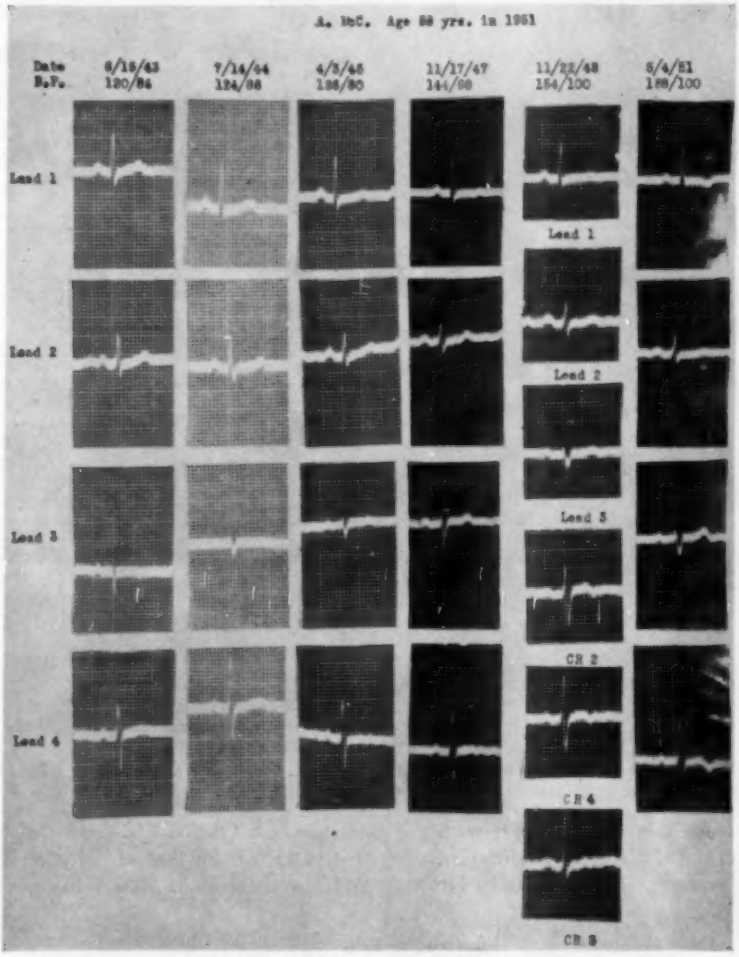


FIG. 2. Mild hypertensive disease.

based on correlation with history and clinical findings, and points to the difficulty of assessing the strain pattern in some patients by the electrocardiogram alone (figure 5). Rheumatic aortic disease was the etiologic factor in left heart strain found in three workers, one of whom required a transfer to lighter work at the age of 65 years. One instance of the strain

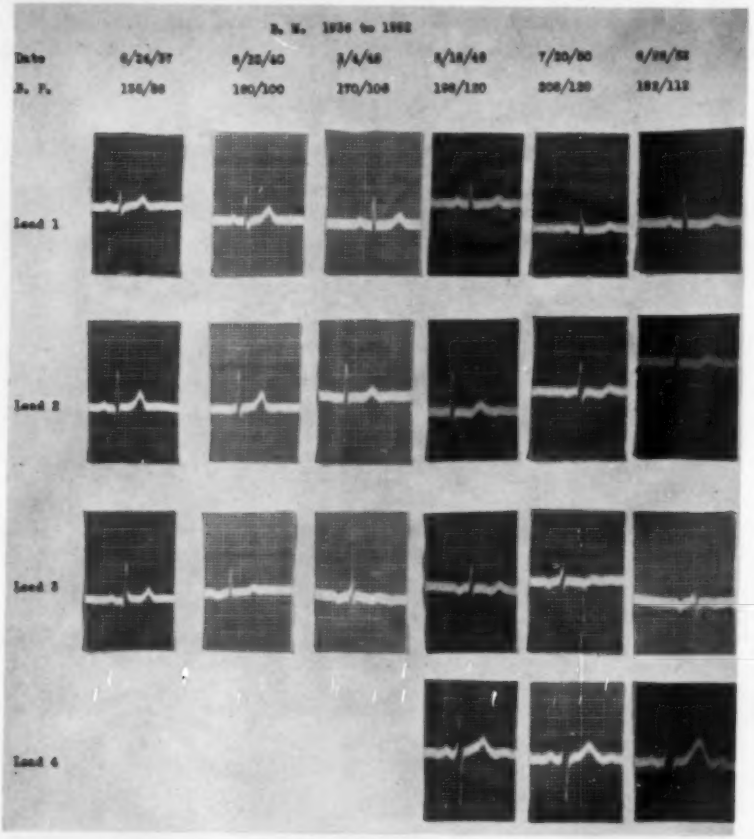


FIG. 3. Progressive hypertension. Height 69½ inches, weight 155 pounds. Age 64 yrs. in 1952. Working as labor foreman.

pattern in a vertical heart with the existence of a Q_2 and Q_3 illustrated the occasional difficulty in differentiating this pattern from that of old posterior infarction. Here the unipolar limb and six chest leads would have been of aid.

Four workers showed a gradual improvement in the strain pattern over the years; again, no quantitative correlation could be seen between the

degree of electrocardiographic alteration and the clinical state. One patient showed disappearance of the pattern with onset of clinical failure, another lost the pattern following successful surgical treatment for thyrotoxicosis, and one severe strain pattern in a young individual prompted a search for and established the diagnosis of coarctation of the aorta.

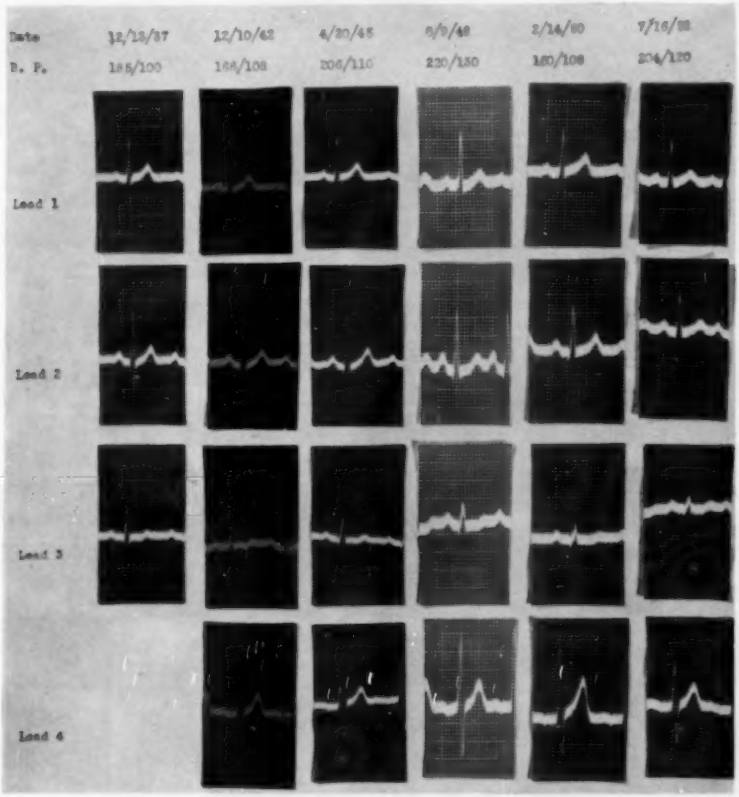


FIG. 4. Persistent hypertension for 15 years without electrocardiographic changes. 1952—cardiac failure and inability to work full-time.

The value of a single Lead IVF or CR_4 frequently was negated when the technician failed to place the electrode beyond the transitional zone to pick up left ventricular potential, or when the latter was missed because of vertical heart position. Conversely, the single chest lead may be arbitrarily and incorrectly recorded as abnormal because of a low, inverted or diphasic T_4 in many individuals. These records were usually in young workers where vertical heart position, or possibly persistence of the juve-

nile electrocardiographic pattern, prevailed (figure 6). With the increasing use of multiple chest leads in the later years of this study, several instances of strain showed the first evidence of this ill-defined and incompletely understood electrocardiographic pattern in the T wave of Lead V_6, with limb lead changes in subsequent years.

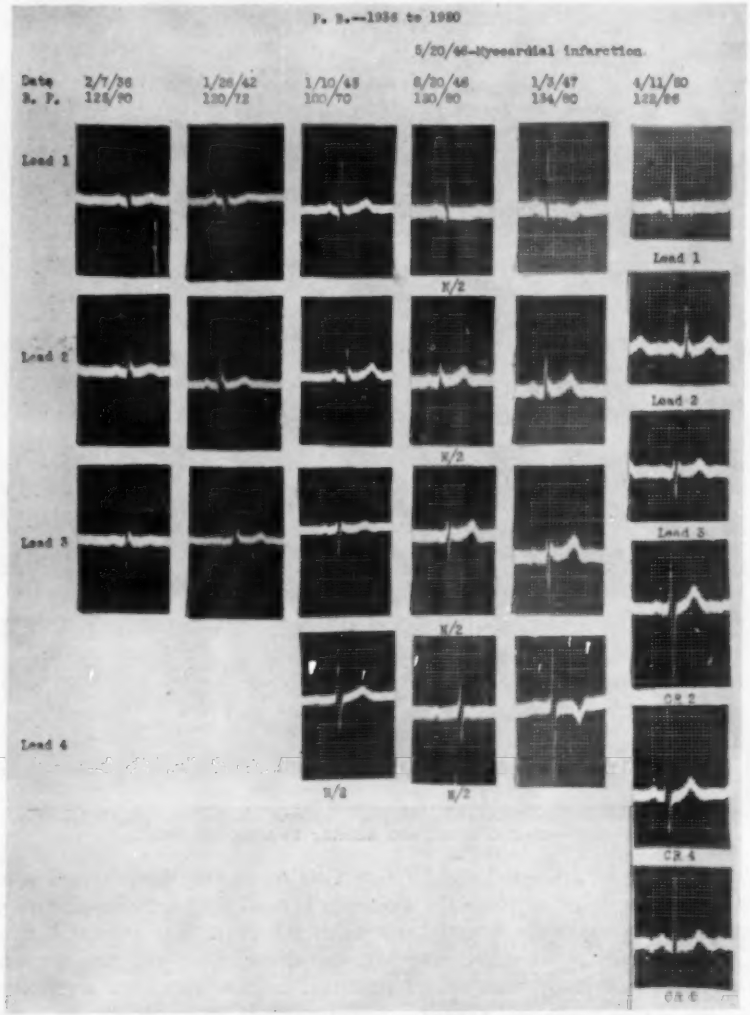


FIG. 5. Example of myocardial infarction resulting in strain pattern only. Worked four years following attack.

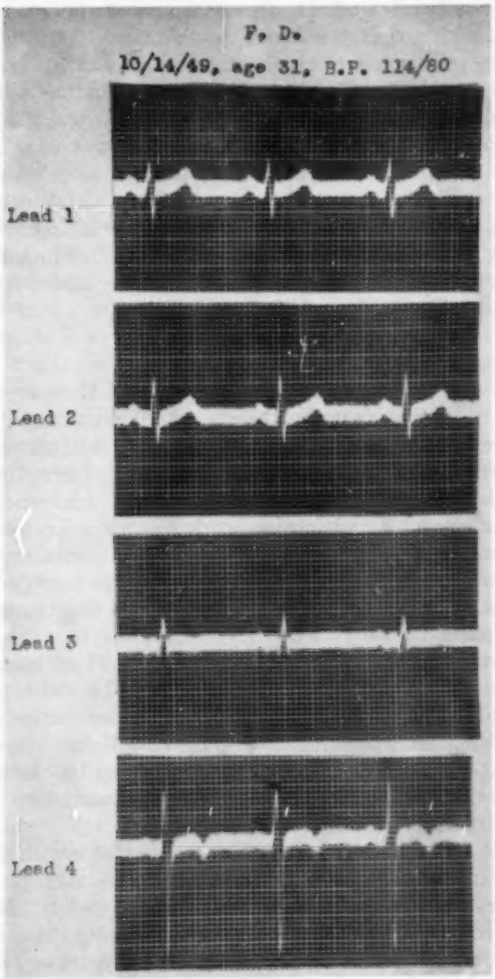


FIG. 6. Example of T_4 inversion so frequently seen when only a single chest lead is used. Normal tracing.

In the opinion of the authors, a minimum of three chest leads (such as CR or $V_{2\text{-}4\text{-}5}$) is necessary for the recognition of varying potentials from both ventricles in routine electrocardiography for industrial personnel. Ideally, all six positions are advised. While electrode placement may vary, the likelihood is great that at least the fourth or the fifth position will reflect left ventricular potential.

In the majority of workers, the existence of the strain pattern was not associated with a change in work classification. Usually, the employee was advised to see his family physician for control of his body weight and blood pressure. We feel that some leniency should be permitted in the interpretation of electrocardiograms in individuals over 50 years of age.[3] With increasing age, there was observed in many workers a tendency for gradual lessening in T_1-T_4-T_5 amplitude, plus some axis shift to the left, without clinical disease and without impairment of job performance. In most workers with normal body weight no electrocardiographic change appeared during advancing age. Hagen and Freeman [4] found that "T-wave changes are not a necessary accompaniment of aging and most old men have perfect electrocardiographic records."

Infarction

Of 51 cases of myocardial infarction with clinical recovery (all males), diagnosed by rigid criteria only, there were 20 acute anterior infarctions, 15 acute posterior infarctions, eight old posterior infarctions and eight old anterior infarctions. Those identified by routine tracing but with inadequate medical history to substantiate the time of occurrence have had an average of 6.2 years of satisfactory work history since the electrocardiographic diagnosis. This figure is an incomplete measure of the post-infarction work record of the 16 men involved, since the infarcts were present for an unknown period of time before the diagnostic electrocardiograms were taken.

In the group of 51 workers whom we believe to have sustained an infarction and recovered, 14 subsequently have died (usually with further myocardial infarction, occasionally with congestive failure or a cerebral vascular accident) after working an average of 3.3 years (ranging for from five months to eight years) following the first recognized infarction. These 14 men lived an average of 3.8 years after the infarction (averaging six months in retirement).

The follow-up on the group of 37 survivors shows that 22 men were still working at the time of the review. They have averaged slightly more than five years at work since infarction was diagnosed. Six others were living in retirement an average of nine years following the diagnosis of their myocardial infarction (working an average of 6.5 years and living in retirement an additional 2.5 years). Two men retired immediately following their acute infarction and were living two and eight years later, respectively. Seven left employment in the company after working an average of two years in the post-infarction period. Their subsequent history is not known.

The average survival for 44 workers who recovered from infarction and whose subsequent history is known is at least 5.2 years. This figure will be increased by an unknown quantity, since 30 of the men are alive, 22 of whom are in productive work. Furthermore, since in 16 of the group

the exact date of infarction is lacking, average survival time existing at the date of the survey is actually higher than the figure of 6.2 years, since elapsed time was measured from electrocardiographic recognition of the infarction in this group. Are these cases truly examples of infarction? To the best of our knowledge they must be so considered. Only classically typical patterns were accepted, omitting those which could be categorized as heart strain or otherwise diagnosed.[2]

Our observations deal only with those workers with myocardial infarction who recovered (four months' survival or longer). Of 16 patients whose infarction occurred eight to 16 years ago, exactly half are still living; in the entire group (including infarctions occurring up to one year prior to the survey), it is known that at least 70 per cent are living.

In the Eastman Kodak Company experience [5] 71 per cent of the living post-infarction employees were working at the time of their survey. Those employees who returned to work and subsequently died worked an average of 4.5 years. There were 95 post-infarction employees still at work when the Eastman survey was made. Seventy-nine per cent of this group had worked from a few months to five years. Fourteen per cent had worked five to 10 years, and 6 per cent had worked more than 10 years.

Weiss and Gray [6] found from private practice in Louisville that 76 per cent of 435 patients who lived more than two months after their first myocardial infarction were able to return to work (including business and professions). The average duration of economic activity after infarction was 4.4 years. A five-year work study showed that 37 per cent of those who returned to work stopped work (by death or retirement) within five years. Twenty-seven per cent of the group who returned to work died within the period of study, after an average duration of life of 4.5 years.

In 1940 Master and Dack [7] found that only 53 per cent of their patients returned to work following recovery from coronary artery occlusion. Among the reasons given for not working were "advice not to work and disability insurance." By 1951 Master and Jaffe [8] found that about two fifths of patients with coronary occlusion regained a state of satisfactory physical function. Sixty per cent of those with satisfactory recovery were working full time and 23 per cent were doing moderate or part-time work. (Average duration of follow-up was 6.5 years.) It would appear that either opportunities for employment or the attitude of physicians and employers regarding employability of the man who has recovered from coronary occlusion may have changed since the 1930's. These and other factors possibly influenced the above increase in rate of employment after recovery. Master and Jaffe [8] concluded that, "instead of discouraging patients who have recovered from a coronary occlusion from working, the physician should encourage them to resume some form of work as soon as this is physically possible."

The average age of our men at the time of infarction was 53.7 years. Levine and Rosenbaum [9] found the average age for myocardial infarction

in a large group of men to be 53.3 years. Smith [10] found the length of life after myocardial infarction (follow-up studies of six years or less) in several reported series of patients to average 41.1 months. Presumably immediate deaths are included in this average. Those workers in our group who have died lived an average of 45.6 months following infarction. There is certainly no indication in this experience that the act of returning to work adversely influenced the life expectancy of the patient. A study of the case records did not suggest that unusual physical effort or the type of work had any bearing on the occurrence of myocardial infarction or on subsequent complications. One gained the impression from study of case histories that the better morale accruing to the individual who was allowed to work was therapeutically desirable. Of interest in this regard is the finding of Morris and Heady [11] that skilled, semi-skilled and unskilled workers in "light" work have twice the mortality from coronary heart disease as do such workers in "heavy" work. Since their mortality figures involved 2,500,000 men, there is some basis for their conclusion that physical work appears to be a way of life conducive to good health. Common sense points to the precaution of removing those individuals with known coronary artery disease from jobs wherein sudden recurrence of symptoms may prove unduly hazardous to the worker or to others.

The prognosis in myocardial infarction, as to both mortality and subsequent ability to work, is undoubtedly much better than some studies based on hospital statistics would indicate. Baer, Heine and Krasnoff [12] found a mortality of only 8.5 per cent within the first six weeks of illness in 182 patients treated at home. Diagnoses were confirmed in these patients by electrocardiograms. Three fourths of the patients were men. Metropolitan Insurance Company follow-up in 540 males with myocardial infarction revealed that 70 per cent were alive at the end of five years, 50 per cent at the end of 10 years, and 43 per cent at the end of 12 years.[13]

Bundle Branch Block

In 20 workers with right bundle branch block (confirmed by multiple chest leads), 18 developed asymptomatically and resulted in no change of employment status. One worker gave a history of acute "collapse" nine months before his block developed, although a tracing taken one month after the "collapse" was normal. He is still working. The other worker who could not be classified as asymptomatic had known liver disease and mild hypertension. The longest known duration of right bundle branch block in this group was 11 years, during which time the employee worked continuously until retirement. The youngest worker, who was 22 years of age, had no clinical evidence of heart disease.

Of 10 individuals who are still working (excluding several who left employment for non-medical reasons), right bundle branch block has been present without symptoms for an average of 4.5 years to date. We found

no correlation between blood pressure readings and this electrocardiographic abnormality. Only one worker had been given a trial of nitroglycerin for possible anginal syndrome. We were impressed by the failure of the block to produce syncope or to add to the hazard of continued employment. The fact that only two of 20 workers with right bundle branch block were found to have symptoms or signs which could possibly be related to that abnormality, after repeated investigation, lends weight to the clinical concept of benign bundle branch block.[14]

Ten instances of S-type intraventricular conduction block (QRS .12 second or longer without change in the intrinsic deflection in multiple chest leads) were discovered. None of these could be correlated with clinical evidence of heart disease in the workers. Two men, age 23 and 33 years, showed this pattern for two years but left the company for non-medical reasons, and one individual of 37 years has been working for two years. The remaining seven men have worked an average of 5.6 years to date with this pattern and without limitation of activity. In those with normal sinus rhythm in the earlier tracings, the change to S-type block occurred asymptomatically. It is possible that accidental discovery of this conduction disturbance in young individuals may represent a benign congenital variant in the conduction system. In those who developed the block in later life, it would appear that employability and prognosis fall near the normal range.

In contrast to right bundle branch and S-type blocks, 10 out of 14 instances of left bundle branch block were associated with clinical heart disease. Six workers with this abnormality had hypertension, three had had myocardial infarction, and one had rheumatic heart disease. Two apparently well individuals could not be followed beyond one year. Two individuals of 61 and 67 years became physically limited and required pensioning one year after developing left bundle branch block. Five employees who are still working have exhibited this pattern for an average of five years to date. From this limited experience there appears to be a greater chance of finding clinical disease and a poorer work prognosis in men with left bundle branch block than in those with right bundle branch block.

Hypertension with a Normal Electrocardiogram

Ten workers with persistent hypertension of several years' duration were found to have a normal electrocardiographic pattern throughout the period of observation. They worked at full employment for an average of 12.1 years after the finding of hypertension, and two are still employed. Figure 4 illustrates one of this group; after 15 years of hypertension he is now in congestive failure. One can only speculate as to what his course might have been with surgical treatment in the earlier years. Observations on these few workers tend to confirm the relatively favorable prognosis in some hypertensive patients, and point to the need for long-term studies on such patients outside of hospitals, where there is selection on the basis of

symptoms. Leishman [15] found that half of a group of 218 hypertensive patients below 60 years of age and with diastolic pressure of 100 mm. of Hg or more had normal electrocardiograms.

O'Hare and Holden [16] reported on 100 patients with benign hypertension followed for an average of 17 years. Although 67 per cent were females, they were impressed with the relatively benign prognosis and reported 71 per cent alive at the end of the study. (Twenty-three patients had lived an average of 25 years with hypertension.) Only 15 per cent of the total group showed strain and/or hypertrophy. Progressive lowering of the T waves in limb leads occurred in half of their group. One can only speculate on the reason for failure of the electrocardiogram to show the expected changes in other patients; possibly a balanced right and left ventricular hypertrophy, or the integrity of the individual's myocardium, is responsible (figures 3 and 4).

Auricular Fibrillation

Twenty instances of auricular fibrillation were discovered by routine tracings. Three were paroxysmal, one was associated with possible acute rheumatic fever; four had normal rhythm for a time but became permanent "fibrillators" later. Ten workers showed long-standing fibrillation averaging 4.4 years. One man whose fibrillation followed rheumatic fever served 12 years in limited employment; another worked as a laborer for the same length of time with this arrhythmia.

In only one worker did fibrillation result directly in disability pension. This was recommended because of embolic phenomena. The remaining workers with auricular fibrillation were able to continue employment. In three cases the fibrillation was preceded by frequent premature auricular contractions during the years when sinus rhythm was present. That auricular fibrillation can occur as a purely functional arrhythmia has received more attention in the last few years. Hanson and Rutledge [17] estimated that approximately 6.5 per cent of patients with this arrhythmia have normal hearts. In spite of this aspect, however, auricular fibrillation is a finding which calls for investigation for the presence of rheumatic carditis, hypertensive disease, coronary arteriosclerosis and hyperthyroidism. As part of the clinical evaluation of these patients we urge an adequate medical study of their ability to work.

Other Observations

Seven instances were found of the Wolff-Parkinson-White syndrome.[18] Four of these showed constant electrocardiographic changes, one persisting for six years and another for eight years. Two workers showed transient episodes of this congenital conduction defect. One showed a mixed pattern with some normally conducted beats after exercise. It is interesting to note that, in 1940, an 18 year old boy with this electrocardiographic abnormality was disqualified for hazardous work on the diagnosis of bundle branch

block. The correct evaluation was made in 1942 and permission given for unlimited employment. No episodes of paroxysmal tachycardia were reported by these workers, in contrast to the observation that two out of three patients with this conduction variant seen in a cardiac clinic may show paroxysms of tachycardia.[18]

Exercise tracings were used occasionally to obtain objective evidence of coronary insufficiency in individuals with suspected angina pectoris. As pointed out by Block et al.,[19] the men with normal resting tracings had the more favorable prognosis. One employee with angina worked for 12 years, finally retiring at age 72! After retirement, his resting electrocardiogram was still normal but the exercise tracing was characteristic of myocardial ischemia. In the absence of severe hypertension, cardiac enlargement or conduction disturbance, many employees with the anginal syndrome worked for several years. Fifteen workers with the anginal syndrome worked an average of 5.4 years after that diagnosis was made.

Five instances of paroxysmal auricular tachycardia were seen, two without recognized heart disease and three with heart disease. One individual had had a previous myocardial infarction; no substernal pain occurred during his bout of tachycardia.

There were 60 workers whose records showed first degree heart block in that the P-R interval was greater than .20 second. Most of these persisted through the years without evidence of disease and without appreciable increase in the A-V conduction time. A few showed shortening of the interval by deep breathing, others by the sitting position. An occasional worker had a P-R interval as long as .28 to .32 second with no other evidence of disease. A history of possible rheumatic fever was obtained in few of these cases. This group of records raises a question on the need to revise the standards of normal A-V conduction. Certainly no disease could be detected in these cases except for one individual who had had adult rheumatic fever.

A careful study of the P waves was of little value in suggesting mitral disease. It became apparent that notching of the P waves tends to occur in the later years and is without clinical significance. Two examples of marked *P-mitrale* (broad and notched P wave deflection) were seen, however. Inversion of P_2 and P_3 with a moderately short P-R interval of about .12 second was found in five records. This has been reported as coronary sinus rhythm and is thought to be due to the origin of the impulse in the tail of the sinus node. None of these workers showed cardiovascular disease. In two men, this pattern was of intermittent occurrence.

Discussion

The electrocardiogram is a helpful adjunct in the evaluation of an employee's health and ability to work. However, it must be used in conjunction with other clinical findings. Phillips, Chapman and Goerke [20]

evaluated 14 different diagnostic procedures for their usefulness in detecting heart disease in workers. The electrocardiogram in their hands was the best single technic for case finding. The 12 lead record detected 65 per cent; the three standard leads, 57 per cent of the cases. Of no little importance is their finding that the electrocardiogram was responsible for 13 per cent of "false positives," i.e., erroneous diagnosis of heart disease. In the survey of Dawber and associates [21] on 2,000 individuals, 140 (50.7 per cent) out of 277 subjects with heart disease were missed when screened by using Lead I alone. The 12 lead tracings, strangely, were no better for screening clinical heart disease except that they had a lower rate of "false positives" in the normal group. Ten per cent of the clinically normal group had doubtful or abnormal records with 12 lead electrocardiograms. With Lead I alone 19.7 per cent of the normal group were judged to be doubtful or abnormal. We are impressed by the necessity of avoiding undue emphasis on minor electrocardiographic abnormalities in order not to jeopardize the individual's future in holding a job. Furthermore, even when definite disease is suggested by electrocardiogram, it is necessary to obtain other and more relevant information on functional capacity in order to arrive at an estimate of the patient's proper work classification.

We found no useful place for a rigid work classification based on tracings alone such as Sprague [22] suggested. Admittedly, he was dealing with a special group: railway transit workers. In his report, retirement may be recommended on the basis of fibrillation, bundle branch block, strain, or inverted T_2 and T_3. In connection with the latter, two men in our group, not discussed above, revealed an inverted T_2-T_3 pattern continuing from 1936 to 1952. Both continue to work at ages 59 and 71 years, respectively, without significant physical incapacity.

Aside from its value to the physician in the recognition and evaluation of arrhythmias, conduction defects and altered blood supply to heart muscle, the electrocardiogram is helpful in getting the coöperation of the patient. Whereas the evaluation of circulatory efficiency may rest largely on other evidence, the tracing per se unquestionably impresses the average worker. It assures him that he has been examined. He is apt to be more receptive to recommendations made in his behalf after such records are taken.

The best use of the worker's productive capacity following the clarification of his cardiovascular functional status from time to time rests largely with others. The physician must be able to define the work attitude and capacity as well as the type of job suited to the individual worker. The employer must have reason, usually from experience, to accept and apply the physician's recommendations on the patient's prognosis and work capacity. Organized labor must find ways to correlate the rights of the handicapped worker with those of seniority and related considerations in the over-all interest of the union membership. The administrators of compensation laws must learn about and accept the nature of degenerative vascular disease as one basically unrelated to either sporadic or prolonged

physical activity per se. If competent medical testimony is sought and accepted, the workmen's compensation laws can be administered fairly, serve their accepted purpose and not act as a bar to the proper employment of the physically handicapped worker.

Acceptance for employment of workers with known cardiac disease and the continued employment of such men are important matters in view of the prevalence of the various forms of cardiovascular disease. It seems unwise to load the enormous economic burden of this group as nonproductive units onto the backs of the younger workers who are clinically free of disease. There is no substitute for the careful clinical evaluation of the individual worker.

Summary and Conclusions

1. We have examined the work record and longevity of a group of industrial workers showing electrocardiographic abnormalities.

2. Serial electrocardiograms are useful in showing alterations in cardiac mechanism, conduction and ventricular strain and in demonstrating myocardial ischemia and necrosis.

3. The electrocardiograms were of little help in determining etiology of heart disease, of no value to prognosis or functional capacity.

4. The records aided appreciably in reassuring the worker with inconsequential signs and symptoms, and in obtaining his coöperation for treatment or modification of working and living habits in the presence of potential or actual heart disease.

5. Myocardial infarction is not infrequently an unrecognized episode and has a better prognosis than some hospital statistics indicate.

6. There is no evidence in this study that physical labor or unusual effort predisposed to myocardial infarction or worsened hypertensive disease.

7. Working capacity rests on the clinical evaluation of circulatory function and the worker's training, not on the electrocardiogram.

8. Under proper job placement and satisfactory mental and emotional states the prognosis of the worker with degenerative vascular disease is equal to or better than that of the man who ceases work immediately upon recognition of his disease.

9. It is suggested that management, labor unions, industrial compensation commissions, and others who are concerned with the best use of the productive capacities of handicapped workers become better acquainted with the issues involved and the natural history of cardiovascular disease.

10. Limited physical capacity may mean reduced productivity and, in turn, reduced income. Is this not better than no economic rehabilitation?

BIBLIOGRAPHY

1. Burch, G. E., and Winsor, T.: A primer of electrocardiography, 2nd Ed., 1949, Lea & Febiger, Philadelphia.

2. Katz, L. N., and Weinstein, W.: The electrocardiogram in axis shift and heart strain, M. Clin. North America **31**: 172-181 (Jan.) 1947.

3. Simonson, E., and Keys, A.: The effect of age and body weight on the electrocardiogram of healthy men, Circulation **6**: 749–761 (Nov.) 1952.
4. Hagen, P., and Freeman, Z.: The electrocardiogram in old age, M. J. Australia **1**: 499–503 (Apr. 15) 1950.
5. Crain, R. B., and Misal, M. E.: The industrial employee with myocardial infarction—his ability to return to work, Arch. Indust. Hyg. and Occup. Med. **1**: 525–538 (May) 1950.
6. Weiss, M. M., and Gray, W. R.: Employability of man after acute myocardial infarction. The ultimate prognosis of 344 men who returned to work, South. M. J. **44**: 312–317 (Apr.) 1951.
7. Master, A. M., and Dack, S.: Rehabilitation following acute coronary artery occlusion, J. A. M. A. **115**: 828–832 (Sept. 7) 1940.
8. Master, A. M., and Jaffe, H. L.: Complete functional recovery after coronary occlusion and insufficiency, J. A. M. A. **147**: 1721–1726 (Dec. 29) 1951.
9. Levine, S. A., and Rosenbaum, F. F.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction: II. Ultimate prognosis, Arch. Int. Med. **68**: 1215–1231 (Dec.) 1941.
10. Smith, C.: Length of survival after myocardial infarction, J. A. M. A. **151**: 167–170 (Jan. 17) 1953.
11. Morris, J. N., and Heady, J. A.: Mortality in relation to the physical activity in middle age, Brit. J. Indust. Med. **10**: 245–254 (Oct.) 1953.
12. Baer, S., Heine, W. I., and Krasnoff, S. O.: The mortality of acute myocardial infarction in private practice, Am. J. M. Sc. **222**: 500–505 (Nov.) 1951.
13. Metropolitan Information Service, "Vastly encouraging," Indust. Med. and Surg. **19**: 508 (Nov.) 1950.
14. Vasifdar, J. P., and Levine, S. A.: Benign bundle branch block, Arch. Int. Med. **89**: 568–574 (Apr.) 1952.
15. Leishman, A. W. D.: The electrocardiogram in hypertension, Quart. J. Med. **20**: 1–12 (Jan.) 1951.
16. O'Hare, J. P., and Holden, R. B.: Longevity in benign essential hypertension, J. A. M. A. **149**: 1453–1457 (Aug. 16) 1952.
17. Hanson, H. H., and Rutledge, D. L.: Auricular fibrillation in normal hearts, New England J. Med. **240**: 947–953 (June 16) 1949.
18. Wolff, L., and White, P. D.: Syndrome of short P-R interval with abnormal QRS complexes and paroxysmal tachycardia, Arch. Int. Med. **82**: 446–467 (Nov.) 1948.
19. Block, W. J., Jr., Crumpacker, E. L., Dry, T. J., and Gage, R. P.: Prognosis of angina pectoris, J. A. M. A. **150**: 259–264 (Sept. 27) 1952.
20. Phillips, E., Chapman, J. M., and Goerke, L. S.: Relative values of techniques used in detection of heart disease, Am. Heart J. **45**: 319–330 (Mar.) 1953.
21. Dawber, T. R., Kannel, W. B., Love, D. E., and Streeper, R. B.: The electrocardiogram in heart disease detection, Circulation **5**: 559–566 (Apr.) 1952.
22. Sprague, H. B.: Employment of cardiacs, Indust. Med. **17**: 279–282 (Aug.) 1948.

FACTORS CONCERNED IN THE GENESIS OF CARDIAC ARRHYTHMIAS *

By Alfred M. Wedd, M.D., F.A.C.P., and Stephen M. Tenney, M.D.,
Rochester, N. Y.

The production of delirium cordis by coronary artery ligation or electrical stimulation of the ventricle was known long before Vulpian [1] by faradization converted the normal systole of either auricle or ventricle into the tremulous movement which he called fibrillation. In 1887 MacWilliam [2] demonstrated that this phenomenon was entirely muscular and that "heightened irritability" and delayed conduction were essential to its production. Through the years there have been many theories for the genesis of cardiac arrhythmias, two of which continue to receive attention, namely, reëntry of impulses and ectopic pacemakers. Mines [3] showed that what he called a circulating excitation, already known in the hearts of lower orders, could occur in the mammalian heart, and suggested that such might be the mechanism of paroxysmal tachycardia and fibrillation in man. Following up that suggestion, T. Lewis and his collaborators [4] in a series of papers presented experimental and clinical evidence that fibrillation and flutter were due to circus movements. Although there was early dissent, the circus theory was widely accepted until recent years, when the genesis of arrhythmias was again subjected to investigation. Prinzmetal and colleagues,[5] using an oscillograph and high speed cinematography to observe and record induced arrhythmias, proposed as a result of their study a unitary theory of atrial arrhythmias according to which each is initiated by an electrical, mechanical or chemical stimulus which sets up an ectopic focus discharging at a given rate, and the rate of discharge determines which arrhythmia will occur.

In recent observations on the cold-blooded heart under the influence of aconitine, Tenney and Wedd [6] have related the multiple response which may follow a single extra shock, and which resembles spontaneous flutter or fibrillation, to concomitant alterations in heart muscle activity. The significance of depressed rhythmicity and conductivity, shortened refractory period and the precise placing of the extra shock in the "vulnerable period" which coincides with the relative refractory period, was emphasized. Conversely, during periods of high spontaneous rhythmicity, or when maximal muscle recovery had occurred following contraction, multiple response to a single stimulus was never seen, even with greatly increased shock strength. Figure 1 illustrates typical reactions of a turtle auricle following aconitine

* Received for publication April 29, 1954.
From the Departments of Medicine and Physiology, University of Rochester School of Medicine and Dentistry. Experimental observations cited are from work done under a grant from the National Institutes of Health, National Heart Institute.

nitrate, concentration 1:100,000. A: Five minutes after the drug had been added there was a slow spontaneous rhythm; a single extra shock (S) placed 0.630 sec. after the normal beat caused a single response, while a shock 0.485 sec. after a normal beat was followed by multiple response. B: Eight minutes after aconitine there was standstill, with no sign of spontaneous pacemaker activity, but the atria would respond to frequent extra shocks; double shocks (S_1, S_2) spaced .365 sec. apart caused single responses; when a second shock was placed .235 sec. after the first there was a double response. C is continuous with B; still closer spacing of the second shock, 0.220 sec., resulted in multiple response.

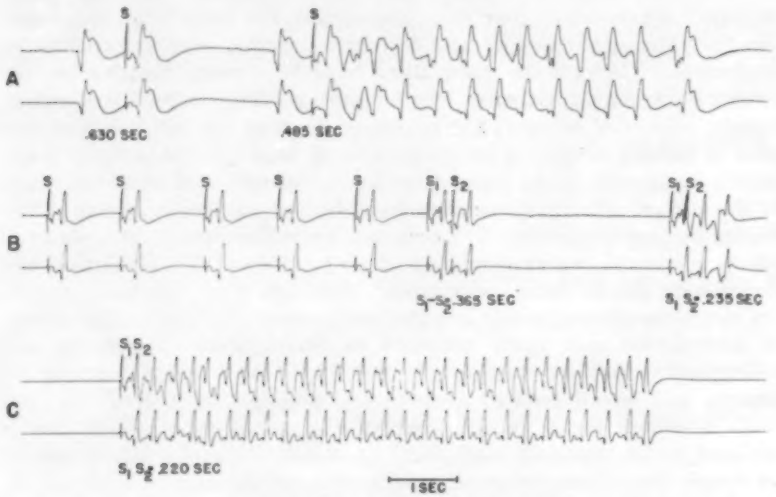


FIG. 1. Responses of turtle auricle under aconitine to electric shocks. Note relation of type of response to timing of extra shock. B and C are continuous and recorded during atrial standstill. Details in text.

The clinical counterpart of the foregoing is known. Abnormal rhythms may arise when normal rhythmicity and conductivity are depressed and the refractory period is shortened, and the relation to a "vulnerable" period is often apparent in clinical cases. In both experimental and clinical instances some overlapping may occur, but in general the multiple response reaction occurs when the abnormal impulse appears early, before the recovery process is completed. Examples are presented in the following case reports:

CASE REPORTS

Case 1 (figure 2). A 65 year old man who had had complete heart block for one month was admitted to hospital because of recurring syncopal attacks. Three different mechanisms were found responsible for syncope: (a) Ventricular standstill;

aside from many short periods, there was one of 90 seconds and one of 125 seconds, shown in line 2. (b) Ventricular tachycardia, line 3. (c) Ventricular fibrillation, line 4. Because of the irregularity of normal ventricular beats and absence of single aberrant beats, the relation of the onset of arrhythmia to normal beats could not be accurately defined; in the illustrations, ventricular tachycardia and fibrillation each appeared approximately 0.6 second after the preceding normal beat. The case illustrates the appearance of abnormal rhythms at a time of severely depressed intrinsic rhythmicity.

Case 2 (figure 3). A 68 year old woman who had had heart block for 10 years was brought to hospital, also because of frequent syncopal attacks. Earlier electrocardiograms showed atrial fibrillation, with periods of idioventricular rhythm. Those illustrated were taken when she was having a convulsion every few minutes. The

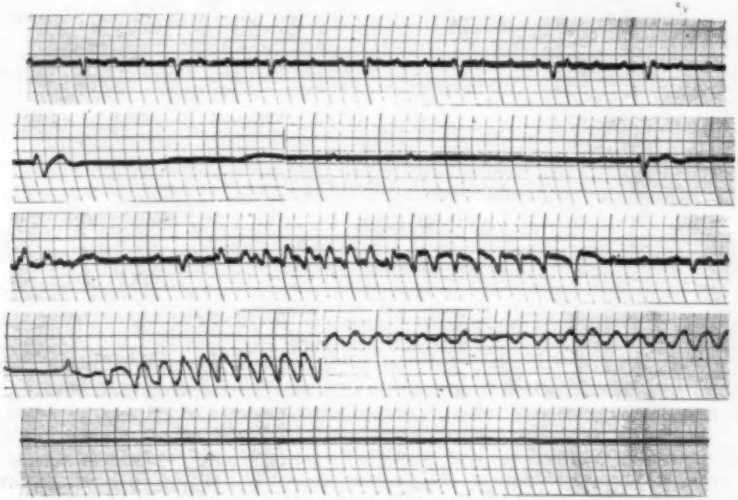


FIG. 2. Illustrating case 1. Top line, complete A-V block. Line 2, ventricular standstill; interval between the two ventricular beats shown was 125 seconds. Line 3, ventricular tachycardia. Line 4, ventricular fibrillation. Line 5, recorded shortly before death, small atrial waves at rate of 30 per minute.

time relationship to the preceding normal beat as a factor in the determination of a single or multiple response is quite clearly indicated, though some overlapping occurs. An abnormal impulse appearing approximately 0.64 second or later is followed by a single response. When the new impulse appeared 0.58 second to 0.64 second after the normal beat, the response was often multiple. The paroxysm of ventricular fibrillation which began toward the end of line B lasted for approximately 20 seconds, when regular idioventricular rhythm returned for a short period. Shortly before the beginning of line C, 1 gm. of potassium chloride was given intravenously, to be promptly followed by slowing and then a return of ventricular fibrillation at a slower rate and death.

Case 3 (figure 4). A 54 year old factory worker was sent to the medical department of his plant for an electrocardiogram at the time he was having chest pain.

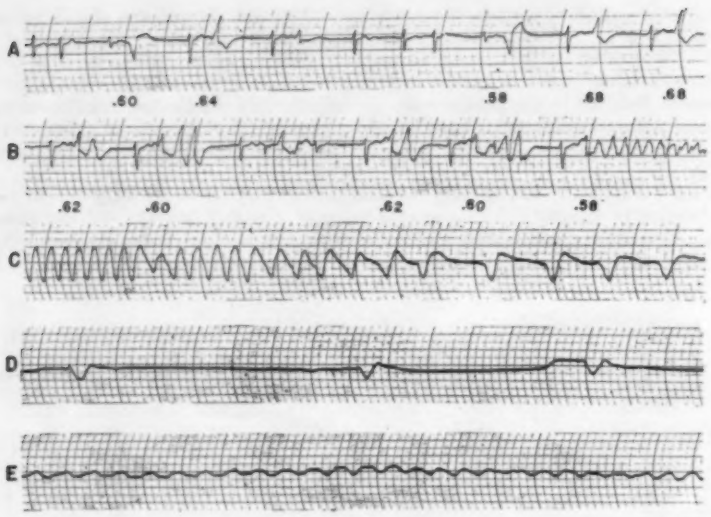


FIG. 3. Illustrating case 2. Note relation of frequency of abnormal responses to appearance time after preceding normal beat. Onset of ventricular fibrillation at end of line B. Lines C, D and E were recorded after 1 gm. of potassium chloride.

Cardiac pain had been intermittent during the preceding 18 hours. During the taking of the record a single aberrant ventricular beat appeared at the peak of a T wave and was immediately followed by ventricular fibrillation and death; the normal Q-T interval was 0.35 second; the abnormal beat appeared 0.26 second after the preceding normal beat, that is, in the "vulnerable period."

Case 4 (figure 5). A 20 year old Negro woman delivered a normal infant at full term. Tachycardia appeared immediately post partum. "A" shows this to be a sinus arrhythmia, with a rate of approximately 160 per minute. Quinidine sulfate, .25 gm., was administered intravenously by the intern, and records B and C, which are continuous, were recorded 20 minutes later. Nodal rhythm, the onset of ventricular fibrillation and a period of atrial standstill are seen. Further slowing and ventricular standstill followed. Postmortem examination disclosed a structurally

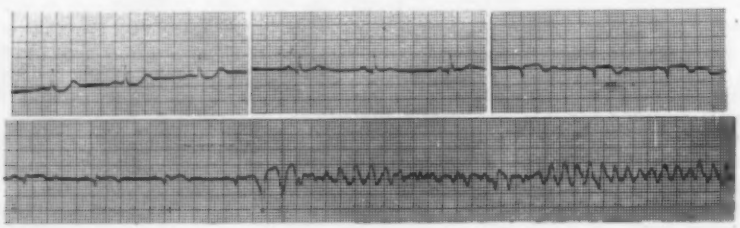


FIG. 4. Illustrating case 3. Onset of terminal ventricular fibrillation during "vulnerable period" in a case of myocardial infarction.

normal heart. Extensive small bowel necrosis secondary to volvulus was also found. The possibility that release of potassium from the large necrotic area might have contributed to the development of the abnormal rhythm was considered, but chemical support was not available.

In both experimental preparations and in man many factors are known that favor the appearance of abnormal rhythms. The ability of the autonomic nervous system, and of drugs that mimic it, to condition the development of heterogenic rhythms has been extensively studied. The importance of anoxia has been recognized experimentally and is doubtless a frequent factor in man. In experiments with turtle atria similar to those in which the effect of aconitine was studied, the multiple response reaction was at times obtained following exposure to nitrogen when it had not been elicited during the control period with oxygen; or if multiple response had occurred during the control period, the duration of the arrhythmia tended to be longer

FIG. 5. Illustrating case 4. A. Sinus arrhythmia, rate 160 per minute. B and C. Continuous, taken 20 minutes after 0.25 gm. quinidine sulfate.

under nitrogen. Rhythmically driven strips of turtle ventricle exposed to an atmosphere of nitrogen showed prolongation of conduction time and shortening of refractory period, the latter shortened by approximately 30 per cent in experiments done at room temperature. The relation of altered electrolyte balance to the appearance of arrhythmias has also been studied. Recently, Harris et al.[7] considered the role of potassium in the development of ventricular arrhythmias in the dog following experimental myocardial infarction, and concluded that excess potassium is an excitant of ectopic activity. As no concept of ectopic activity was expressed by those authors, it is desired here merely to point out the depressant effects of excess potassium, seen both in heart muscle and in nerve tissue. When driven strips of turtle ventricle were bathed in a solution containing three times the normal potassium content of Ringer's solution, marked depression of conductivity followed promptly. The depressant action of potassium on the human ventricle is illustrated in case 2. In certain crustacean nerves, normal repetitively firing axons became non-repetitive within a few seconds after

being placed in solutions containing excess potassium chloride.[8] It may also be noted that in figure 2 of the Harris paper the relation of the duration of multiple response to the time of onset is well shown; the longest response began earliest in the cardiac cycle.

Those alterations in heart muscle activity known to occur concomitantly with arrhythmias do not appear conducive to the formation of new foci of high rhythmicity which may function as pacemakers. That localized areas of profoundly altered muscle may permit reëntry has already been considered.[6] As to the demonstration of localized pacemakers by cinematography, it should be mentioned that Mines recognized that ordinary electrical or mechanical recording would not discriminate between a series of spontaneous beats and a continuing wave of excitation. He emphasized the need for cinematographic recording, but from his observations concluded that a circulating excitation was the underlying mechanism of the arrhythmias he studied. The circus theory as Lewis left it may today be inadequate, but it was only a special application of the larger concept of reëntry of impulses in heart muscle, and for the latter there is much factual support. Aside from the question of new pacemakers, there is the important role of the altered muscle state in the intensification of the "vulnerable period," during which the arrival of an extra cardiac stimulus may set off an abnormal rhythm. Such a sequence would seem a frequent possibility for the production of arrhythmias in man. Knowledge of the part that may be played in their production by anoxia, nerve influences or various chemical agents must be taken into account in attempting to prevent or treat arrhythmias in clinical practice.

Summary

Concomitant alterations in heart muscle activity, such as depression of rhythmicity and conductivity, shortening of refractory period, and enhancement of the "vulnerable period" which coincides with the relative refractory period, have been considered in relation to the genesis of cardiac arrhythmias.

Experimental observations on the turtle heart under the influence of aconitine and spontaneously appearing arrhythmias in clinical cases have been cited to illustrate the relationship to altered muscle activity. Such evidence supports the concept of impulse reëntry as a mechanism for the production of arrhythmias.

The part played by functional alterations in muscle activity in the production of arrhythmias will need to be considered in procedures designed to prevent or to treat arrhythmias in clinical practice.

BIBLIOGRAPHY

1. Vulpian, A.: Sur les effets de la faradization des ventricules du coeur chez le chien, Compt. rend. Soc. de biol. **26**: 394, 1874.
2. MacWilliam, J. A.: Fibrillar contraction of the heart, J. Physiol. **8**: 296, 1887.

3. Mines, G. R.: On dynamic equilibrium in the heart, J. Physiol. **46**: 349, 1913.
4. Lewis, T., et al.: Observations upon flutter and fibrillation, Heart **7**: 1920.
5. Prinzmetal, M., Corday, E., Brill, I. C., Oblath, R. W., and Kruger, H. E.: The auricular arrhythmias, 1952, C. C Thomas, Springfield, Ill.
6. Tenney, S. M., and Wedd, A. M.: Disturbances of rhythm in the cold-blooded heart under aconitine, Circ. Res. **2**: 28, 1954.
7. Harris, A. S., Bisteni, A., Russell, R. A., Brigham, J. C., and Firestone, J. E.: Excitatory factors in ventricular tachycardia resulting from myocardial ischemia. Potassium a major excitant, Science **119**: 200, 1954.
8. Wright, E. B., Coleman, P., and Adelman, W. J.: Effect of potassium on the crustacean single motor nerve fiber, Federation Proc. **13**: 168, 1954.

THE SELECTIVE USE OF ANTICOAGULANTS IN ACUTE MYOCARDIAL INFARCTION BASED ON INITIAL PROGNOSIS *

By Morton M. Halpern, M.D., Louis Lemberg, M.D., Martin Belle, M.D., and Herbert Eichert, M.D., F.A.C.P.,
Miami, Florida

Reliable evidence accumulated in the last 10 years has indicated that anticoagulants are of decided value in the prevention and treatment of thromboembolic diseases. Beginning with Wright's report in 1945,[1] the specific value of anticoagulants in the management of acute myocardial infarction has been adequately demonstrated by many investigators.

The advisability of instituting anticoagulant therapy in every case of cardiac infarction has been challenged recently.[2-5] Inconvenience, expense, and certain known hazards inherent in anticoagulant therapy were stated to outweigh any benefits that might accrue from its use in the so-called "good risk" cases. One report [6] goes even further, by concluding that the outcome of the "very poor risk" as well as of the "good risk" patient with acute myocardial infarction is not altered by anticoagulants. Unfortunately, in most studies the prognosis was estimated in retrospect with a review of hospital records after the outcome of the individual cases had been established. In other words, the actual separation of patients into "good risk" and "poor risk" categories was not done early, at which time institution of appropriate therapy might have affected the prognosis materially. On the other hand, the prognoses of both Littmann's [3] and Wright's [7] series of cases apparently were classified as good or bad initially. Unfortunately, they arrived at opposite conclusions. Littmann agreed with Russek in that the "serious complications occurred in the patients who were sickest at the onset," whereas Wright stated that the outcome could not be predicted during the first 24 hours with any degree of accuracy.

Our approach to this problem was to accept the consensus that anticoagulants are definitely indicated in the "poor risk" cases, and to reject the suggestion that they have no place in the therapy of acute myocardial infarction.[8] Even if we were to accept the contention that "good risk" cases of myocardial infarction could do as well without as with anticoagulants, there still remains the crucial question, Can the clinician determine whether the patient has a good or bad prognosis during the early stages of an acute coronary occlusion?

* Received for publication January 4, 1954. Presented at the Regional Meeting of the American College of Physicians, St. Simons Island, Georgia, October 17, 1953.
From the Departments of Cardiology, Jackson Memorial and Mercy Hospitals, Miami, Florida.

Methods And Materials

A form was completed in each case of acute myocardial infarction when seen initially. The examining physician recorded such pertinent points as history of previous infarctions, heart failure and thrombo-embolism; also, the degree of pain, the severity of shock, the presence of heart failure, and the type of arrhythmia during the attack were noted. An estimation of the prognosis of the case was made when the patient was first examined and again in 24 and 48 hours.

A group of clinicians who handled the individual patients, including resident hospital physicians, general practitioners and internists, volunteered to fill out these forms. The estimation of the prognosis was purely an uninstructed personal opinion of the doctor handling the case. He recorded it as belonging either to a "satisfactory" or to a "poor risk" category. The term "satisfactory risk" is used synonymously with "good risk" in this paper. The patients were from private or staff services. They were neither consecutive nor selected. The records were reviewed by the authors when the clinical course and subsequent outcome were available.

The choice of anticoagulants was left to the individual physician. Almost without exception Dicumarol was used, and occasionally Tromexan. In many cases Heparin was administered initially until a therapeutic level was obtained. One case received Heparin alone throughout the hospital course.

Control of Heparin therapy was effected by frequent determination of the Lee-White clotting time. Usually an attempt was made to keep it 30 minutes or above. Control of Dicumarol or Tromexan dosage was by daily prothrombin times performed by the Link-Shapiro modification of the Quick method utilizing both the dilute and undilute values. The usual contraindications to anticoagulant therapy were followed. Mortality in this series refers to death while still being treated in the hospital.

With this routine, 167 cases were collected; however, 50 were discarded as unsatisfactory, leaving 117 which fulfilled the criteria for the diagnosis of acute myocardial infarction. The 10 who died within the first 24 hours of admission were also omitted, because it is highly unlikely that anticoagulants could have altered their outcome. These deaths were due mostly to intractable shock and pulmonary edema. The remaining 107 cases were then analyzed.

There was nothing unusual in the age and sex distribution. Males predominated over females 3.1 to 1 and, as expected, the mortality was greater in the older age groups. Russek and Zohman [9] were the first to point out that this increased mortality in the older patients was due to a higher incidence of severe attacks in later life. According to them, the mildly ill among the older patients did just as well as those in the younger age group.

Results

Since the prognosis was estimated by the physician as soon as the patient came under his observation and again in 24 and 48 hours, the results afforded us an opportunity to observe how reliable the judgment of the clinician was in the separation of the "satisfactory" from the "poor risk" cases (table 1). Significantly, six patients were changed from a "satisfactory" to a "poor risk" category during those 48 hours. Four subsequently died. Twenty-four cases were transferred from "poor" to "satisfactory." Three of these died. One was admitted as a "satisfactory" case, then changed to "poor" in 24 hours, and back to the "satisfactory" classification in 48 hours. Thus, in 29 per cent of the 107 cases the attending physicians felt it necessary to reverse their initial decisions. From this it would seem that it is difficult, if not impossible, to form an accurate opinion of the prognosis of acute myocardial infarction in the early stages. Wright [7] also recently emphasized that the outcome could not be predicted initially. Consideration of these findings suggested that a 48 hour period of observation

Table 1

Change in Prognosis during the First 48 Hours

	Cases	Died
Satisfactory to poor	6	4
Poor to satisfactory	24	3
Satisfactory to poor to satisfactory	1	0
Total	31	7

29.0% of 107 cases changed prognosis in first 48 hours

was the most desirable upon which to base prognosis, and such a plan was followed in this study.

Corrections were made in the initial prognosis because of previous infarction or heart failure which, as will be shown, indicates a poor outlook. These changes could be made in retrospect without impairing the study. As a result, 11 "satisfactory risk" cases were transferred to the "poor risk" classification. After the above corrections the "satisfactory risk" cases, both with and without anticoagulants, had a mortality of 5.1 and 5 per cent, respectively (table 2). On the other hand, the "poor risk" cases had a mortality of 25.6 per cent. This is exclusive of the deaths in the first 24 hours. In contrast, there was a 60.0 per cent mortality of the "poor risk" cases of Russek et al.[2] Littmann [3] noted a 15.9 per cent mortality in his group of male "poor risk" patients treated with anticoagulants. The over-all mortality of our series was 14.0 per cent exclusive and 21.4 per cent inclusive of those who died in the first 24 hours. Thus, according to this study, the determination of the prognosis at the end of 48 hours appears to be fairly reliable, since of those classified as "satisfactory" risks, only

5 per cent died. Furthermore, it would seem that anticoagulants are of only questionable value in these "satisfactory risk" patients, since their subsequent course was not significantly altered regardless of whether they received anticoagulants.

We considered next the features of the medical history which might be of value in estimating prognosis (table 3). Angina pectoris was not a significant factor affecting prognosis in our series, since we found that of

TABLE 2

	59 Satisfactory Risk		48 Poor Risk		Total			
	Cases	Died	Cases	Died	Cases	Died		
Received anticoagulant	39	2(5.1%)	43	11(25.6%)	82	13(15.8%)	14.0%	21.4%
No anticoagulant	20	1(5.0%)	5	1(20.0%)	25	2(8.0%)		
Died during the first 24 hours						10		

the 41 patients who had a previous history of angina, six died (14.6 per cent). Levine and Rosenbaum [10] felt that angina pectoris might even improve the immediate outlook because of the presence of an improved collateral circulation. Doscher and Poindexter,[11] on the other hand, thought it was an unfavorable influence.

A previous myocardial infarction raised the mortality significantly. Of 24 who had such a history, seven died, a mortality of 29.2 per cent. Others have reported a higher death rate.[12] As a corollary, it might be

TABLE 3

History of	Cases	Deaths	Mortality
Angina	41	6	14.6%
Myocardial infarction	24	7	29.2%
No infarction	56	5	8.9%
Hypertension	26	4	15.4%
Diabetes	5	0	0
Heart failure	5	2	40.0%

stated that the death rate is low in the absence of previous infarction: five of 56 cases in this group died, a mortality of 8.9 per cent. This is similar to the results of other studies.[13]

In our patients a history of hypertension did not significantly alter the mortality. Although a record of the previous blood pressure is not always obtainable, we did obtain a history of hypertension in 26 patients. Four of these died, a mortality of 15.4 per cent. Some investigators [10, 11, 12] noted that hypertensives have a higher mortality rate. Nay and Barnes [14] stated

that patients with a history of hypertension are more likely to have a cerebral vascular accident during convalescence but less apt to have a second infarction. Yater et al.[15] noted that the blood pressures of their surviving patients were higher, which they thought indicated a greater ability to adjust to the circulatory needs.

The importance of a history of heart failure in increasing the mortality has been mentioned by others.[12] Our experience confirmed this, since of the five patients we encountered with a history of heart failure two died. There has been insufficient emphasis on previous congestive failure as a poor prognostic sign.

According to Russek,[2] a history of pulmonary embolism or thrombophlebitis should also be considered as a serious sign. This is undoubtedly true, and it should be considered as an absolute indication for anticoagulant therapy.

At the time of the acute attack the size of the infarction is probably the most important factor in determining the mortality.[16] Unfortunately,

TABLE 4

The acute attack	Cases	Deaths	Mortality
Shock—mild	33	4	12.1%
Severe	7	2	28.6%
Pain—mild	46	4	8.9%
Severe	61	5	8.5%
Pulmonary edema	8	4	50.0%
Arrhythmia	24	5	20.8%

this cannot be estimated clinically with any degree of accuracy. Nevertheless, the signs and symptoms about to be discussed are to a great degree related to the size of the infarcted area.

Shock, when severe, is usually followed by a high mortality; two out of seven in our series died, a mortality of 28.6 per cent (table 4). Pain appeared to be unimportant in determining the prognosis. This is in agreement with other studies [10, 12] except for that of Russek et al.,[2] who considered intractable pain a poor prognostic sign.

It is generally agreed that frank acute pulmonary edema is an ominous sign. Of eight cases, 50 per cent died, the same mortality noted by Master, Dack and Jaffe.[17]

A serious cardiac arrhythmia has been alleged to constitute a poor prognostic sign,[2, 10, 18] but this was not evident in our study. Master et al.[17] also considered this to be an insignificant manifestation. Nevertheless, the appearance of ventricular tachycardia undoubtedly indicates a poor prognosis.

Other serious signs mentioned in the literature are pericardial friction rub, diastolic gallop,[10] shock plus failure, diabetes, azotemia,[6] rapid pulse, a

pulse pressure less than 20 mm. of mercury, muffled or tic-tac rhythm, cyanosis, a respiratory rate over 28 per minute, fever over 101 degrees,[17] clammy perspiration, hiccups, a cloudy sensorium, a leukocytosis over 15,000 [12] and bundle branch block.[10] The relative value of these signs has never been established, but to a great extent they are all manifestations of the size of the myocardial infarction.

Complications are the major problem during the period of convalescence following the acute attack. Thrombo-embolism is one of the most significant of these complications, and its accurate diagnosis is difficult. This is borne out by the great variation in its reported incidence. Nay and

TABLE 5

	107 Cases									
	59 Satisfactory Risk Cases				48 Poor Risk Cases					
	39 Received Anticoagulant		20 None		43 Received Anticoagulant		5 None			
	No.	Died	No.	Died	No.	Died	No.	Died	Total	Died
Thrombo-embolism	2 (5.1%)	1	0	0	5 (1.6%)	1	0	0	7 (6.5%)	2 (28.6%)
Recurrence or spread of infarction	1 (2.6%)	1	1 (2.6%)	1	4 (9.3%)	1	0	0	6 (5.6%)	3 (50.0%)
Heart failure	2 (5.1%)	2	3 (15.0%)	1	20 (46.5%)	7	0	0	25 (23.4%)	10 (40.0%)
Bleeding	4	0	0	0	1	1	0	0	5 (4.7%)	1 (20.0%)
Absent QRS changes	5	0	9	0	3	1	0	0	17 (15.9%)	1 (5.6%)

Barnes [14] reported its occurrence in 37 per cent of 100 cases of acute myocardial infarction, whereas Doscher and Poindexter [11] stated that it was diagnosed in only 6.5 per cent of the 414 cases they presented. Certainly the diagnosis of pulmonary embolism, unless it be large and typical or confirmed by postmortem studies, is always a problem. Pneumonitis and left ventricular failure are often misdiagnosed as pulmonary infarction, especially when the index of suspicion for thrombo-embolism is high. In any case, a certain amount of caution is necessary when determining the incidence of thrombo-embolic phenomena. It presented a problem to us when reviewing the charts, but we were satisfied of its presence, either pulmonary or peripheral, in seven cases (6.5 per cent), with two deaths (table 5). It occurred in two of 59 "satisfactory risk" cases (5.1 per cent),

and in five of 48 "poor risk" cases (11.6 per cent). The over-all death rate due to thrombo-embolism was only 1.9 per cent. These figures are lower than those of Wright.[7]

Spread of infarction during convalescence was reported by Nay and Barnes [14] in 15 per cent of their 100 consecutive cases. Selzer [19] stated that 2 to 3 per cent die from secondary infarction. The diagnosis was made in six patients (5.6 per cent) in this series (table 5). Two were "satisfactory risk" and four were "poor risk" cases. Two of the former and one of the latter died of that complication, a mortality of 50 per cent. The true value of anticoagulants in preventing and treating this particularly ominous complication has yet to be definitely established.

A history of heart failure or its occurrence during the acute attack is a serious sign. When it occurs during convalescence it is equally significant. Twenty-five cases developed heart failure during the hospital course, and of these 10 (or 40 per cent) died during hospitalization (table 5). Again,

TABLE 6

Time of Admission after Onset

	Cases	% of Total	Mortality
Within 24 hours	81	75.7%	15
Within 48 hours	8	7.5%	0
48 hours to 7 days	5	4.7%	0
Over 7 days	5	4.7%	0
Time indefinite	8	7.5%	0
	107	100.0%	

the largest proportion of these patients were in the "poor risk" category. In the series of Yater et al.,[20] of 54 patients who died during the hospital course, 13 had congestive failure. Wooten [21] reported a 71.9 per cent mortality when congestive heart failure occurred with myocardial infarction.

Bleeding due to anticoagulant overdosage was not a significant complication in this series of cases. Four "satisfactory risk" cases were recorded as having gross hematuria, and one "poor risk" patient died with hemorrhage from a ruptured abdominal aneurysm. The part that anticoagulants played in the latter episode is uncertain.

Levine and Rosenbaum [10] pointed out that patients with "less striking" electrocardiographic changes have a distinctly better outlook. It was significant to us that, of 17 cases whose 12 lead electrocardiograms failed to show QRS changes, only one died, and that one from the abovementioned ruptured aortic aneurysm. Also, nine of the 20 "satisfactory risk" cases without anticoagulants belonged to this group. This feature probably signifies a small infarction and consequently a better prognosis. There were no cases in this group of marked, widespread electrocardiographic RS-T

segment depressions indicative of massive subendocardial infarction. Such a case may have a poorer prognosis in the absence of QRS changes and, consequently, would be an exception.

Determination of the time interval between onset and admission showed that the majority of our cases were admitted during the first 24 hours (table 6). Russek et al. found that 60 per cent of the cases they reviewed entered the hospital during the day of the attack. Of the deaths in our series, all were admitted during the first 24 hours. This is in direct contrast to the findings of Billings et al.,[12] who found the 30 day mortality higher when more than one day elapsed before the patient came to the hospital. They state also that admission more than 96 hours after the onset improved the prognosis. It is felt that, at least in our 107 cases, there may have been a natural, unintended selection of "good risk" cases, in that they were not considered sufficiently ill for hospitalization during the early hours of the attack. Whether this is generally true remains to be demonstrated. In the home-treated cases reported by Baer, Heine and Krasnoff,[22] there was the low mortality of 8.5 per cent. It was noted that 166 of the 182 cases were first attacks. This attests to the fact that they probably consisted mostly of milder cases. At the other extreme there must be many cases that die before hospitalization is achieved or even before they are seen by a physician. Features such as these make mortality statistics of acute myocardial infarction difficult to interpret.

Summary

1. In 117 cases of verified acute myocardial infarction the prognosis was recorded immediately, 24 and 48 hours after the onset by the examining physician.

2. Of these 117, 10 (8.5 per cent) died within the first 24 hours of admission and were not included, leaving 107 in the study.

3. During the first 48 hours there was a change in prognosis from "satisfactory" to "poor" in six cases, with four eventually dying. Twenty-four were transferred from "poor" to "satisfactory," with three deaths. Thus, 29 per cent of 107 cases had a change in prognosis during the first 48 hours.

4. Of 82 receiving anticoagulants, 15.8 per cent died. Eight per cent of the 25 not receiving anticoagulants died.

5. "Satisfactory risk" patients as judged at the end of 48 hours had a mortality of 5 per cent with or without anticoagulants. The "poor risk" cases had a mortality of 25 per cent.

6. The most significant features in the history which should automatically place the patient in a "poor risk" category are previous myocardial infarction and heart failure. A history of thrombo-embolism is undoubtedly a bad prognostic sign.

7. The most ominous signs of the acute attack are severe shock and

acute pulmonary edema. Intractable pain may contribute to the shock. The general appearance of the patient is also of great importance.

8. Absent QRS changes in the 12 lead electrocardiogram indicate a "satisfactory" risk, barring the serious signs mentioned above or the diagnosis of massive subendocardial infarction.

9. No deaths occurred in those admitted after the first 24 hours of the attack, suggesting that a natural selection had taken place in that they probably were not considered ill enough initially to be admitted to the hospital.

Conclusion

We conclude from this study that it is impossible to determine the prognosis of an acute myocardial infarction during the first 48 hours of the attack with enough accuracy to justify the withholding of anticoagulants unless the onset was 48 or more hours previous to the initial observation. In the latter case, enough crucial hours have elapsed to make a safe estimate of the prognosis which, if satisfactory, would justify the withholding of anticoagulants. In all of the other cases it is recommended that anticoagulants be administered initially for at least two days, until a more accurate prognosis can be established. After that the anticoagulants may be withdrawn in those considered to have a good prognosis.

BIBLIOGRAPHY

1. Wright, I. S.: Experiences with Dicumarol in the treatment of coronary thrombosis, Proc. Am. Federation Clin. Research **2**: 28, 1945.
2. Russek, H. I., Zohman, B. L., White, L. G., and Doerner, A. A.: Indications for bishydroxycoumarin (Dicumarol) in acute myocardial infarction, J. A. M. A. **145**: 390, 1951.
3. Littmann, D.: The prevention of thrombo-embolism in acute coronary-artery disease, New England J. Med. **247**: 205, 1952.
4. Schnur, S.: Mortality and other studies questioning evidence for and value of routine anticoagulant therapy in acute myocardial infarction, Circulation **7**: 855, 1953.
5. Furman, R. H., Gale, R. G., Billings, F. T., Jr., and Meneely, G. R.: Critical appraisal of anticoagulant therapy with Heparin and Dicumarol in coronary arteriosclerosis with myocardial infarction by comparison within prognostic categories, Am. J. Med. **7**: 133, 1949.
6. Furman, R. H., Ball, C. O. T., Gale, R. G., Billings, F. T., and Meneely, G. R.: An evaluation of anticoagulant therapy in myocardial infarction based on prognostic categories, Am. J. Med. **14**: 681, 1953.
7. Wright, I. S.: An evaluation of anticoagulant therapy, Am. J. Med. **14**: 720, 1953.
8. Feldman, L., O'Connor, W. R., Friedman, I. A., and Fischer, J. W.: Anticoagulant therapy in acute myocardial infarction, Am. Heart J. **44**: 112, 1952.
9. Russek, H. I., Zohman, B. L., Doerner, A. A., Russek, A. S., and White, L. G.: Age and survival in cases of acute myocardial infarction, J. A. M. A. **147**: 1731, 1951.
10. Levine, S. A., and Rosenbaum, F. F.: Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction. I. Immediate prognosis, Arch. Int. Med. **68**: 913, 1941.

11. Doscher, N., and Poindexter, C. A.: Myocardial infarction without anticoagulant therapy: deaths, emboli and an analysis of factors influencing mortality, Am. J. Med. **8**: 623, 1950.
12. Billings, F. T., Jr., Kalstone, B. M., Spencer, J. L., Ball, C. O. T., and Meneely, G. R.: Prognosis of acute myocardial infarction, Am. J. Med. **7**: 356, 1949.
13. Master, A. M., Jaffee, H. L., and Dack, S.: The treatment and immediate prognosis of coronary artery thrombosis, Am. Heart J. **12**: 549, 1936.
14. Nay, R. M., and Barnes, A. R.: Incidence of embolic or thrombotic processes during immediate convalescence from acute myocardial infarction, Am. Heart J. **30**: 65, 1945.
15. Yater, W. M., Traum, H., Spring, S., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. P.: Coronary artery disease in men 18–39 years of age, Am. Heart J. **36**: 334, 1948.
16. Ernstene, A. C.: Complications and sequelae of acute myocardial infarction, J. A. M. A. **150**: 1069, 1952.
17. Master, A. M., Dack, S., and Jaffe, H. L.: Coronary thrombosis: an investigation of heart failure and other factors in the course and prognosis, Am. Heart J. **13**: 330, 1937.
18. Smith, J. F., Keyes, J. W., and Denham, R. M.: Myocardial infarction: a study of the acute phase in 920 patients, Am. J. M. Sc. **221**: 508, 1951.
19. Selzer, A.: The immediate sequelae of myocardial infarction: their relation to prognosis, Am. J. M. Sc. **216**: 172, 1948.
20. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Geisler, M. A., and Wilcox, B. B.: Coronary artery disease in men eighteen to thirty-nine years of age, Am. Heart J. **36**: 481, 1948.
21. Wooten, R. L., and Kyser, F. A.: Mortality and treatment of myocardial infarction: a review of 455 cases, Ann. Int. Med. **38**: 247, 1953.
22. Baer, S., Heine, W. F., and Krasnoff, S. W.: The mortality of acute myocardial infarction in private practice, Am. J. M. Sc. **222**: 500, 1951.

PERSISTENT NONHEMOLYTIC HYPERBILIRUBINEMIA ASSOCIATED WITH LIPOCHROME-LIKE PIGMENT IN LIVER CELLS: REPORT OF FOUR CASES *

By HELMUTH SPRINZ, Lt. Colonel, M.C., F.A.C.P., *Washington, D. C.*, and ROBERT S. NELSON, Colonel, M.C., *Fort Knox, Kentucky*

THE more frequent use of needle biopsies in the diagnosis of liver disease has led to the clarification of the pathogenesis in many known clinical conditions. It might be expected that the widespread employment of this procedure would also uncover certain histologic findings which, together with the clinical picture, could not be readily explained under previous concepts. In a total of 630 needle biopsies of the liver performed on the Medical Service of the 98th General Hospital, Munich, Germany, two instances have been noted of unusual biopsy findings which, in our experience, showed no correlation with the initial clinical evaluation of the cases in question. The biopsies were performed in an attempt to diagnose unexplained, long-standing, low grade, nonhemolytic icterus. The gross specimen of liver tissue appeared black when obtained, and histologic examination showed marked storage of a lipochrome-like pigment in liver cells without other evidence of pathologic change. The absence of any significant inflammatory cellular infiltrate or fibrosis was particularly noteworthy. We have since come to recognize the association of a persistent nonhemolytic hyperbilirubinemia with an unusual pigmentation of liver cells and have observed two additional cases at Walter Reed Army Hospital. The clinical and laboratory findings in all instances were sufficiently similar to lead us to believe that we were dealing with a new and heretofore undescribed syndrome.

The purpose of this report is to give a detailed description of these cases so that more data may eventually be accumulated and a better concept of the condition obtained.

CASE REPORTS

Case 1. A 42 year old white woman was admitted to the 98th General Hospital on November 2, 1952, for observation for posthepatitic cirrhosis. She had had two previous episodes of jaundice. The first had occurred at the age of 10, at which time she was jaundiced for four weeks. Her recovery was uneventful. At 20 years of age she was deeply jaundiced over a period of seven months. She ran a fever up to 105° F. and suffered from attacks of colicky upper abdominal pain and nausea throughout the first month of illness. There was no history of exposure to hepato-

* Received for publication March 16, 1954.
From the Medical and Laboratory Services of the 98th General Hospital, Munich, Germany, and Walter Reed Army Hospital, Washington, D. C.

toxic agents. She had had no transfusions, was only a moderate user of alcohol, and had never had any tropical diseases. Family history was noncontributory. While in Japan in September, 1950, she again became deeply jaundiced. She was studied at several hospitals and was finally evacuated to the United States, where she was studied at an Army general hospital. In January, 1951, on the basis of liver function studies, she was told that she probably had posthepatitic cirrhosis. No biopsy was done. She improved subjectively and was finally discharged from the hospital, although she continued to have mild weakness, anorexia, indigestion and some loose stools, with low grade scleral icterus. At the time of admission to the 98th General Hospital, nearly two years after the recurrence of the jaundice, she was largely asymptomatic. Her temperature was normal, pulse 98, blood pressure 130/92 mm. of Hg. Her sclerae were slightly icteric and her tongue was coated. Physical examination was otherwise within the normal range. The liver and spleen could not be felt, and there was no ascites, venous distention or telangiectases. Laboratory examinations showed the urinalysis and blood counts to be within normal limits and the cardiolipin and heterophile antibody reactions negative. Total serum bilirubin was 2.60 mg. per cent, with a one minute reading of 1.12 mg. per cent. Thymol turbidity was 8.0 units, cephalin flocculation negative, Bromsulphalein retention 11.0 per cent (5 mg. per kilogram) in 45 minutes. Total proteins were 7.18 gm. per cent, albumin 4.59 gm. per cent, globulin 2.68 gm. per cent, cholesterol 175 mg. per cent, of which the esterified portion was 62 per cent. Serum amylase was 53 units; stools were negative for blood, ova and parasites, and the culture was negative for pathogenic organisms. X-rays of the chest and flat plate of the abdomen were both negative, but the gallbladder failed to fill on oral dye administration, although no opaque calculi were seen. Clinical course in the hospital during 12 days of observation was uneventful except for persistent scleral icterus. A liver biopsy was performed on the fifth hospital day. The patient left the hospital at her own request and was to return for further studies but failed to do so.

Case 2. A 25 year old white male soldier was admitted to the 98th General Hospital by transfer on May 5, 1952, for observation for chronic hepatitis. On December 13, 1951, he had first noticed general weakness, fatigue and dark urine. One week later he felt abdominal distention which seemed to be due to excess gas. On January 2, 1952, he developed acholic stools and jaundice and was admitted to an Army hospital, where his symptoms gradually subsided during the ensuing four months. The patient felt well and was considered clinically cured. However, just prior to transfer to the 98th General Hospital, the serum bilirubin was still slightly elevated and his Bromsulphalein test revealed 30 per cent retention at the end of 45 minutes. There was no history of hepatotoxins. His alcohol consumption had been approximately three bottles of beer a day, with some cognac on week-ends, and there had been no previous episodes of jaundice or tropical diseases. He had had gonorrhea in 1945 and had been treated with sulfadiazine and two injections of penicillin, with no recurrences. He had also had a car accident in 1944, in which the left clavicle and several ribs were fractured. Following this his left leg had shown intermittent swelling and numbness. He received three immunization injections in December, 1951. There was no history of other injections during the six month period prior to onset of his present illness. Family history was noncontributory. Physical examination on transfer showed a trace of scleral icterus. The liver was enlarged 1 cm. below the costal margin and was nontender; the spleen could not be felt. There was no lymphadenopathy except for a small, nontender node in the left axilla. The left leg showed slight enlargement over the right leg at the thigh and calf. The remainder of the examination was negative. Temperature and pulse were within normal limits, and the blood pressure was 125/80 mm. of Hg. The serum bilirubin on admission was 1.68 mg. per cent total, with a one minute reading of 0.85 mg. per cent, and showed a mild fluctuation during the three months' observation, with a

high of 2.76 mg. per cent total on May 28, 1952, and a low of 1.56 mg. per cent total, and 0.77 mg. per cent one minute on June 10, 1952. Proportionate ratio of total to one minute readings varied little during this period. Thymol turbidity varied from 3.0 to 4.0 units (three tests), and cephalin flocculation was persistently negative (three tests). Bromsulphalein retention was 11.0 and 19.0 per cent on two occasions. Values for urinary coproporphyrins were within normal limits, and serum cholesterol showed totals of 276 mg. per cent (75 per cent esters) and 132 mg. per cent (64 per cent esters) on separate tests two weeks apart. Serum proteins were 6.19 gm. per cent total, albumin 3.59, and globulin 2.60. Serum alkaline phosphatase, 1.9 Bodansky units. Urinalyses and blood counts were within normal limits, as were the bleeding, clotting and prothrombin times. No atypical cells were noted in the peripheral blood smear, reticulocyte counts varied from 0.6 per cent to 2.4 per cent (four tests), and no spherocytes were seen. Red blood cell osmotic fragility was normal, and the Coombs' test was negative. Stools were negative for blood, ova and parasites, and urobilinogen in the stool totaled 84 mg. per 100 gm. of feces. Urinary urobilinogen amounted to 64 Ehrlich units per 24 hours. Sedimentation rates varied during the period of observation, rising during concomitant thrombophlebitis, but returning to normal as the infection subsided. X-rays of the chest were negative. Those of the lumbar spine showed evidence of an old compression fracture of L-1, with some hypertrophic lipping of the lower thoracic spine. On two attempts the gall-bladder failed to fill with the contrast medium (oral dye), but no opaque calculi were seen. Bone marrow aspiration revealed an ME ratio of 2.2:1 on count of 500 cells. No abnormal forms were seen, and the results were judged to be compatible with the reticulocyte count. The patient remained essentially asymptomatic during his entire three month period of observation at this institution except for an episode of mild thrombophlebitis of the left femoral vein, which subsided rapidly on routine measures. He felt well, gained nine pounds, and was up and about with bathroom and mess hall privileges. Two liver biopsies and one skin biopsy were performed. The skin section showed no abnormal pigments and was negative for pathology. Liver size did not vary and there was no tenderness. Because of persistently elevated serum bilirubin over a period of seven months the patient was evacuated to the Zone of the Interior for further studies and disposition. After an additional five months' observation, during which time the clinical, laboratory, x-ray and histologic findings remained unchanged, the patient was discharged from the Army one year after the onset of his illness.

Case 3. A 22 year old white man was admitted to Walter Reed Army Hospital on June 22, 1953, for evaluation of chronic icterus. The patient had entered the service in September, 1952, and had served in Japan and Korea from February through March, 1953. He had had no habits contributory to his medical condition, and his family history was negative for any familial diseases. The patient was essentially well until March 15, 1953, when he developed a sore throat, fever (104° F.), chilly sensations and vomiting. There was no cough and no diarrhea. He was treated with penicillin and apparently obtained a good response. On March 17, two days after the onset of the above symptoms, it was noted that he had yellow sclerae. The patient volunteered the information that he had noted yellow sclerae the year prior to his Army enlistment, and at that time he had had no associated symptoms, such as cold or sore throat. On March 22 he was transferred from Korea to Japan with a diagnosis of hepatitis. He remained until June 16 in an Army hospital in Japan, where he was treated for acute hepatitis. His sclerae alone remained icteric, but his skin at no time showed any clinical jaundice and he was essentially well throughout this hospitalization. During the last month of his hospital stay in Japan his only complaints were mild epigastric discomfort and a sensation of intermittent nausea, which had no particular relationship to types of food. On June 18 he was returned to this country for further hepatitis study. On admission to Walter Reed Army Hospital the patient appeared well. His sclerae were yellow, but other-

wise the physical examination was essentially negative. The liver and spleen were not palpable, nor was there any abdominal tenderness. Biopsies of the skin, muscles, fat, gastric and rectal mucosa, liver and bone marrow were done. The bone marrow showed an occasional deposit of tan-brown, coarse, amorphous pigment granules within reticulum cells which were not further identified but which were considered to be quite similar to the pigment in the liver. Otherwise, the bone marrow aspirate was quite fatty and only moderately cellular, but showed a normal ME ratio. The other biopsies were entirely negative and free of pigment. Liver function tests were essentially normal with the exception of the total bilirubin and the one minute direct bilirubin. Several determinations of the total serum bilirubin were around the 3.0 mg. per cent level, and several determinations of the one minute direct remained around the 2.0 mg. per cent level. Bromsulphalein retention fluctuated between 10 to 17 per cent. The remainder of the laboratory studies, which included numerous blood, urine and stool examinations, heterophil agglutination, red cell osmotic fragility tests and blood chemistries, was essentially negative. The reticulocyte count was 0.4 per cent. Total protein, albumin-globulin ratio, phosphatases, thymol turbidity, cephalin flocculation, phenolsulfonphthalein and Congo red tests, cholesterol and cholesterol esters were all within normal limits. Chest x-ray, gastrointestinal series and urogram were all negative. A gall-bladder series on two occasions showed a nonfunctioning gall-bladder (oral dye). The patient remained essentially well throughout hospitalization. During the early days of his stay he continued to complain of a mild nausea and vague epigastric discomfort. These symptoms cleared spontaneously and the patient was returned to military duty in August, 1953.

Case 4. A 24 year old Puerto Rican male entered Walter Reed Army Hospital on August 13, 1953, for final evaluation of a chronic icterus of 14 months' duration. His present illness dated from early September, 1952, when he had developed headache, nausea, vomiting and increasing fatigue while stationed in Korea. Shortly thereafter he noted discolored brown urine and right upper quadrant pain. He sought medical attention, at which time scleral icterus and fever were noted. His past and family history were essentially noncontributory. There was no familial history of jaundice or anemia, and the patient gave no history of discolored urine or recurrent febrile episodes. He had never had any parenteral medication or transfusions, and there was no history of pruritus.

When admitted to an Army Hospital in Japan on September 16, 1952, his liver was barely palpable and was slightly tender. The spleen was considered palpable. The blood count was normal except for the presence of 21 per cent eosinophils. The icteric index was 12 and the serum bilirubin, 1.5 mg. per cent. Urine was normal. Stool specimens showed *Trichuris trichiura,* hookworm and *Endamoeba histolytica.* The patient was placed on a bed-rest regimen and a high caloric diet, and on September 22 the total serum bilirubin was 1.2 mg. per cent. The Bromsulphalein test showed a trace of dye retention, and the patient was ambulatory. Treatment with Aureomycin was started for amebiasis, but anorexia recurred. On October 9 he became very nauseated and had to be given glucose and thiamine intravenously. His stools remained positive for *E. histolytica,* for which he received a course of chloroquine. On October 21 his icteric index rose to 13 and the serum bilirubin to 2.1 mg. per cent. He was again placed on a bed-rest routine and was given tetrachloroethylene for his hookworm infestation. During the period October 30 to December 18, 1952, total serum bilirubin varied between 1.3 and 3.2 mg. per cent independent of the activity of the patient. Bromsulphalein retention varied from 5 to 16 per cent, and his appetite was poor at times. It was believed that he had chronic hepatitis, possibly superimposed on amebic hepatitis. He was consequently evacuated to the Zone of Interior and arrived at an Army general hospital December 18, 1952.

Physical examination at that time showed: height, 5 feet, 1 inch; weight, 139

pounds; temperature, 98.6° F.; pulse, 80; blood pressure, 134/78 mm. of Hg. The sclerae were slightly icteric, and the liver and spleen were not palpable.

Laboratory and X-ray Findings: Routine hemograms revealed 11,000 white blood cells, with 61 per cent neutrophils, 32 per cent lymphocytes and 7 per cent eosinophils; hemoglobin, 18.5 gm.; sedimentation rate, 5 mm. Stool examinations revealed the presence of ova of *Tr. trichiura*. *E. histolytica* was never identified, and cultures for enteric pathogens were negative. Routine urinalysis and standard serologic test for syphilis were negative. In numerous tests the urine showed occasionally a single specimen positive for bile. Complement fixation for leptospirosis was negative. Reticulocyte count was 1.5 per cent; 24 hour urine urobilinogen revealed a value of 5.6 Ehrlich units. Coombs' test was negative. Complement fixation for amebiasis was also negative. Liver function tests performed on admission revealed a total bilirubin of .8 mg. per cent, a thymol turbidity of 1.6 and negative cephalin flocculation. Total cholesterol was 173, with 54 per cent esters. Alkaline phosphatase, 7.6 units; urine urobilinogen, positive in 1:10 dilution; prothrombin time, normal; total protein, 8.3 gm. per cent, with albumin, 4.9 gm. per cent. On December 29 the bilirubin rose to 3.8 mg. per cent total, with 1.4 mg. per cent direct, and on January 10 was down to 0.8 total and 0.5 direct. It rose again to 2.6 total and 1.5 direct on January 17, and 3.0 total and 1.4 direct on January 24. Repeated weekly determinations revealed a continued fluctuation of the bilirubin values between 1 and 2.5 mg. per cent total. Chest x-ray on December 23, 1952, was negative. Gall-bladder series on March 12, 1953, showed a functioning gall-bladder with no evidence of stones, but on a series taken six days later the gall-bladder failed to fill. Diagnostic biliary drainage yielded the following: "A" bile total of 180 c.c., "B" bile total of 90 c.c., "C" bile total of 120 c.c. No characteristic cholesterol or calcium bilirubinate crystals could be found. Two liver biopsies were performed which initially were reported as showing bile stasis. However, on review it was realized that they illustrated the entity under discussion.

During his entire hospitalization the patient remained ambulatory and was asymptomatic and afebrile. Reëxamination of the patient's abdomen revealed no hepatomegaly and no splenomegaly. He was returned to full duty on April 20, 1953. The patient was well until June 2, 1953, when he was again admitted at another Army hospital with a complaint of poor appetite, jaundice, and pain over the liver area when walking.

Physical examination revealed essentially normal findings except for definitely icteric sclerae and slight tenderness in the right upper quadrant. No definite liver edge was felt on admission.

Laboratory Data: Liver function tests on June 3, 1953: icteric index, 30 units; total serum bilirubin, 3.68 mg. per cent; thymol turbidity, 16.3; alkaline phosphatase, 2.6 units; cephalin flocculation, 3 plus in 24 hours and 3 plus in 48 hours. The day following admission the patient suddenly developed a spiking temperature that rose to as high as 107° F. rectally, and a smear for malaria parasites was positive. In addition, the spleen was palpable to about two fingerbreadths below the left costal margin, but was not particularly tender. The patient was started immediately on chloroquine and his temperature rapidly returned to normal. After the first two or three days of hospitalization he was completely asymptomatic and remained so throughout the rest of this hospitalization. Liver function tests returned to normal, with the exception of the serum bilirubin, which stayed at 2 mg. per cent total. Numerous urinalyses and stool examinations were negative. After six weeks of hospitalization the patient was completely asymptomatic and looked healthy and had gained weight. However, on August 13, 1953, he was sent to Walter Reed Army Hospital because of his persistent hyperbilirubinemia. Physical examination was entirely within normal limits, with the exception of icteric sclerae. The spleen and liver were not palpable.

Laboratory Data: On admission, bilirubin 1 minute, .93 mg. per cent; total, 1.7

mg. per cent; Bromsulphalein test, 7 per cent retention; thymol turbidity, 1.5; zinc turbidity, 5.0; cephalin cholesterol flocculation, 0; protein, total, 8.2; albumin, 4.5; globulin, 3.7; alkaline phosphatase, 4.7 units; cholesterol, total, 187; esters, 72 per cent. Following his admission the laboratory tests stayed at about the same level with the exception of the bilirubin, which fluctuated, the highest value being 3.5 mg. per cent total, and 1.6 mg. per cent 1 minute. Several urine specimens showed a trace of bile but were free of other abnormal constituents. Complete blood counts, osmotic fragility test, direct and indirect Coombs' tests, heterophil agglutinations and special examination of peripheral blood smears showed normal values. Red cell survival studies with chromated red cells indicated normal life span of the patient's cells. Bone marrow examination showed a richly cellular marrow with normal maturation pattern of all hematopoietic elements. There was a moderate erythropoietic hyperplasia of a nonspecific nature. A slight increase in eosinophils—3 per cent in the bone marrow and 9 per cent in the peripheral blood—was noted. Urine urobilinogen was again low normal; fecal urobilinogen was within normal limits. Stool examinations on repeated occasions revealed *Tr. trichiura* but no other ova or parasite. Twenty-four hour urinary coproporphyrin values ranged between 244 and 694 micrograms. The gall-bladder was not visualized with both the usual and the double dosage. The complement fixation test for leptospirosis was negative. A liver biopsy confirmed the findings of the previous biopsy examinations.

Histopathology of Liver Biopsy Specimens

The gross and microscopic findings in all cases were, with minor exceptions, strikingly similar and characteristic, so that once the condition was recognized the diagnosis could be made at a glance. In all cases the operator who obtained the needle biopsy or the pathologist who processed it commented on the black or blackish green color of the gross specimen. This feature was so characteristic that one of us (R.S.N.) made the diagnosis of the entity under discussion in case 2 from examination of the fresh liver biopsy alone. Microscopically, all cases showed the liver architecture to be preserved. The columns of liver cells were intact and well oriented towards the efferent vein. This structure was regular. The liver cells were uniform and of average dimensions (figure 1). The striking and diagnostic feature of the section was the presence of innumerable dark brown, fine to moderately coarse amorphous pigment granules in the cytoplasm of the liver parenchymal cells (figure 2). The pigment was not evenly distributed, being more prevalent in the central zone of the lobule (figure 3). The liver cells containing pigment granules showed different degrees of involvement. While some cells were almost completely filled with pigment, others contained only a single or a few granules. The granules varied in size from dustlike to approximately one fourth the size of a liver cell nucleus. Special stains showed the pigment granules to be negative for iron and bile. They were dissolved by 3 per cent potassium hydroxide and were argentophil. The pigment was unaffected by the fixatives employed, Carnoy's fluid, absolute alcohol, Susa, and neutral formalin. The presence of pigment was unaccompanied by an inflammatory response or by regressive changes of the affected liver cells. Only very rarely, and not always connected with areas of maximal pigmentations, minute foci of liver cell necrosis were noted. The

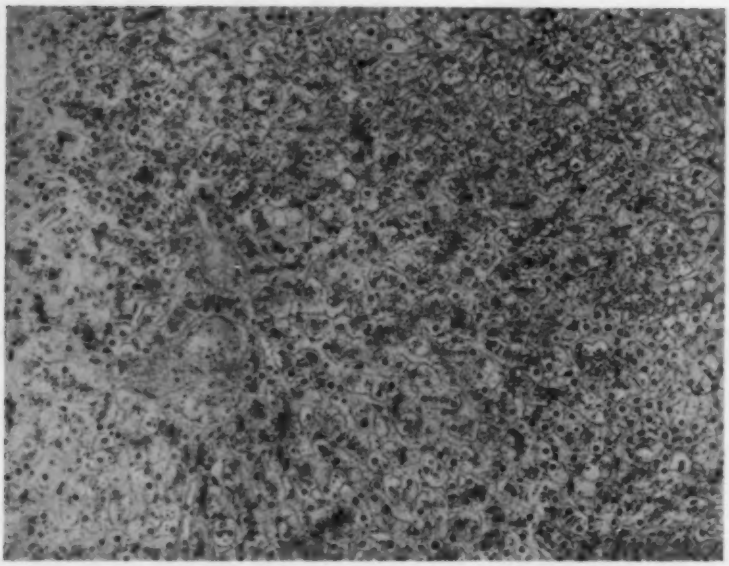


FIG. 1. *Case 4.* Histologic section of liver. A sublobular and central vein is present in the left lower field. Note normal architecture, irregular distribution of pigment within liver cells, lack of inflammatory cellular infiltrate, and absence of fibrosis.

reticuloendothelial cells lining the sinusoids were slightly more prominent than usual. A moderate number of them contained pigment granules identical to those seen in the liver cells. Only very occasionally was a structure seen which could be interpreted as a bile thrombus in a slightly distended bile canaliculus. The periportal fields were essentially regular. The bile ducts showed no evidence of proliferation, but were of regular dimensions and free of content. There was some slight increase of collagenous connective tissue fibrils in the periportal spaces which contained a slightly increased number of lymphocytes and occasional pigmented macrophages. One of the cases also showed a slight to moderate degree of fat vacuolation. Many of the vacuolated cells also contained pigment granules. The distribution of the pigment was similar to other cases. In the two cases in which multiple biopsies were available, the individual accession showed an essentially similar picture, although several months had elapsed between the taking of the specimens. These findings have been confirmed by Dr. I. N. Dubin,[1a] of the Armed Forces Institute of Pathology, Washington, D. C., to whom the material was submitted. Dr. Dubin was able to collect nine additional cases.[1b]

In summary, the pathologic examination revealed as the principal finding an alteration of cellular metabolism, e.g., excessive pigment storage in liver cells. Although the exact nature of the pigment remains undetermined,

we believe it to be an endogenous pigment and have therefore called it lipochrome-like. The strikingly black color brings to mind such heavily pigmented dipyrrylcompounds as mesobilifuscins and copronigrin,[2] but proof of identity of the pigment must await further investigation.

Discussion

Clinical similarities in the cases presented consisted of low grade, persistent icterus without definite incapacitation of the individual. Two of our patients had had similar attacks in the past. The onset of the condition in each case was heralded by a picture closely resembling and clinically judged to be infectious hepatitis, which gradually merged into that of persistent icterus. In each instance it was felt that permanent liver damage of the more usual sort (marked fibrosis, bile stasis necrosis or cellular infiltration) would be revealed in the biopsy specimen, but this was not found. The hyperbilirubinemia was characterized by a relatively high direct serum bilirubin of nearly 50 per cent of the total. The only other persistent laboratory evidence of abnormal function of the liver was mild elevation of the Bromsulphalein retention, which undoubtedly was slightly influenced by the bilirubin elevation. No evidence of abnormal destruction of red blood cells could be obtained. Close questioning of patients failed to reveal any

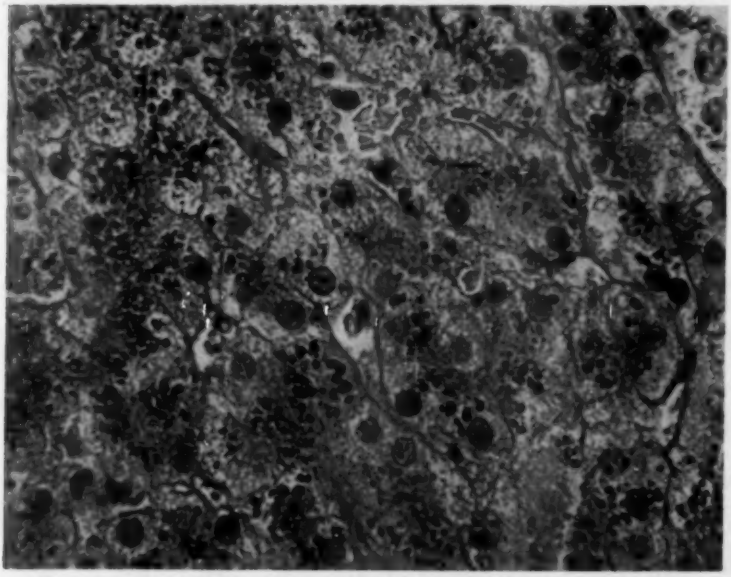


Fig. 2. *Case 4.* Histologic section of liver. Note presence of pigment granules in otherwise regular liver cells.

contact with liver poisons. In all cases the gall-bladder was not visualized by x-ray, although the exact significance of this finding is in doubt.

From the data presented the following conclusions may be drawn: We are not dealing with a chronic persistent hepatitis as understood by pathologists and defined by Himsworth,[3] since our cases fail by a wide mark to show the degree of fibrosis and cellular infiltration necessary to make this diagnosis. We can rule out the diagnosis of cirrhosis, as the liver architecture in our cases is perfectly preserved. The minimal degree of periportal fibrosis and the rare occurrence of minute foci of liver cell necrosis which

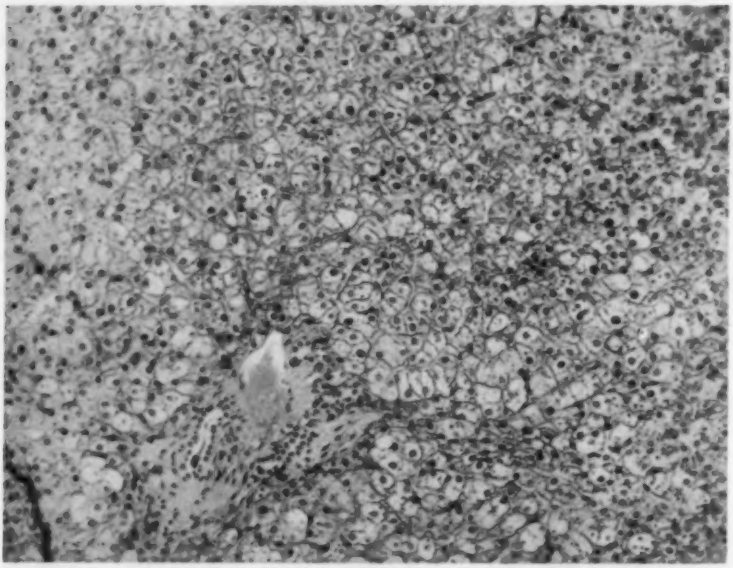


FIG. 3. *Case 4.* Histologic section of liver. A periportal field is present in the left lower field. Note absence of inflammatory reaction and reduction of amount of pigment in the peripheral zone of the lobule.

were exhibited by the four patients are, in our experience, nonspecific, and have so frequently been observed in diverse disease entities that we hesitate to attribute any pathogenetic or etiologic significance to these findings. The unusual pigmentation which characterized the liver biopsy specimens has never been noted as a sequence of an acute parenchymatous hepatitis going into a chronic phase. No mention of a pigmentation of liver cells has been made in the papers dealing with the end results and possible sequelae of viral hepatitis,[4, 5, 6] nor have we seen similar pigment in our own follow-up studies of cases of infectious hepatitis.[7] The histopathologic findings likewise exclude bile stasis or a type of cholangiohepatitis as the cause of the patients' illness. Bile thrombi are rather toxic to liver parenchymal cells

and are not stored in seemingly intact liver cells to the degree exhibited by our patients. If the pigment were bile, some unequivocal bile thrombi should have been formed and the pigment would not have remained in its granular form. Furthermore, our pigment does not give the staining reaction for bile. The periportal fields do not show the fibrosis, cellular infiltration and bile duct alteration associated with cholangiohepatitis of long standing. In the absence of evidence of hemolysis, increased red cell turnover, or altered red cell morphology, we can exclude congenital and acquired hemolytic anemias as being the cause for the persistent hyperbilirubinemia. The pigment in our cases does not give the histochemical reaction of iron. Reports in the literature on so-called constitutional hereditary nonhemolytic hyperbilirubinemia fail to describe the presence of any significant amount of pigment in liver cells.[6, 8] The direct reacting serum bilirubin in this condition is characteristically relatively low in proportion to the total,[9, 10] while in our cases the one minute serum bilirubin amounted to nearly 50 per cent of the total. For these reasons we feel we are not dealing with Gilbert's disease. Our data exclude a hemolytic type of production jaundice or a regurgitation jaundice as the mechanism involved in the entity under discussion.

The association of chronic jaundice with marked pigmentation of the liver cells is felt to be significant in the cases presented. Further study of similar clinical material, with the application of histochemical technics, may in the future reveal the pathogenesis of this syndrome through the medium of the liver biopsy.

We assume that we are dealing with a nonhemolytic, synthetic type of production jaundice in which hyperbilirubinemia results from an inborn or acquired error of metabolism. The final elucidation of this problem must await further knowledge of the nature of the pigment and of the pigment metabolism in persistent nonhemolytic hyperbilirubinemia with hyperpigmented liver cells.

Summary

Four cases of long-standing and, in two instances, recurrent icterus associated with an unusual type of hyperpigmentation of the liver cells are presented. The onset of the condition resembled infectious hepatitis which gradually merged into persistent jaundice without definite incapacitation of the individual. In addition to the elevated serum bilirubin (relatively high direct and low total), the only constant and significant laboratory finding is a slightly increased Bromsulphalein retention. The gall-bladder is nonfunctioning in all cases. Anatomically, the black-brown color of the liver biopsy specimen is striking and is due to storage of a non-iron non-bile pigment, the exact nature of which has still to be determined. There is no concomitant inflammation of the liver parenchyma or bile stasis. The possible pathogenesis of this condition is discussed.

ACKNOWLEDGMENT

We are deeply grateful to Colonel F. W. Pruitt, Lt. Colonel E. D. Palmer, Major I. C. Plough and Captain T. C. Chalmers, of the Medical Service of Walter Reed Army Hospital, for their kind coöperation in making available to us the clinical data on cases 3 and 4, and to Dr. I. N. Dubin, of the Armed Forces Institute of Pathology, Washington, D. C., for his encouragement and advice.

BIBLIOGRAPHY

1. (a) Dubin, I. N.: Personal communication to the authors.
   (b) Johnson, F. B., and Dubin, I. N.: Excessive lipochrome pigment in liver cells in constitutional hyperbilirubinemia, Am. J. Path. **29**: 585, 1953.
2. Gray, C. H.: The bile pigments, *in* Methuen's Monographs on biochemical subjects, 1953, Methuen, London.
3. Himsworth, H. P.: The liver and its diseases, 2nd Ed., 1950, Harvard University Press, Cambridge.
4. Dible, J. H., McMichael, J., and Sherlock, S. V. P.: Pathology of acute hepatitis, Lancet **2**: 402, 1943.
5. Sherlock, S. V. P., and Walshe, V.: The post-hepatitis syndrome, Lancet **2**: 482, 1946.
6. Hult, H.: "Cholémie simple familiale" (Gilbert) and posthepatitic states without fibrosis of the liver, Acta med. Scandinav. **138**: suppl. **244**, 1950.
7. Nelson, R. S., Sprinz, H., et al.: The effect of physical activity on recovery from hepatitis: a follow-up study 2 to 3 years after onset of disease, Am. J. Med. **16**: 780, 1954.
8. Curry, J. J., Greenwalt, T. J., and Tat, R. J.: Familial nonhemolytic jaundice: report of a case with liver biopsy, New England J. Med. **226**: 909, 1942.
9. Comfort, M. W.: Constitutional hepatic dysfunction, M. Clin. North America **29**: 982, 1945.
10. Dameshek, W., and Singer, K.: Familial nonhemolytic jaundice, constitutional hepatic dysfunction with indirect van den Bergh reaction, Arch. Int. Med. **67**: 259, 1941.

OCCURRENCE OF ACCUMULATION OF FAT IN THE LIVER AND ITS RELATION TO EXCESS WEIGHT GAIN IN PATIENTS CONVALESCING FROM VIRAL HEPATITIS *

By Arthur R. Colwell, Jr., M.D., *Chicago, Illinois*

In former biopsy and autopsy studies of the liver in cases of infectious hepatitis, only brief reference to the appearance of fat has been made. The purpose of the present paper is to report the occurrence of this complication in approximately one-half of 144 patients with the disease, from whom a total of 199 liver biopsies were taken. Liver fat was noted mainly in those patients who gained appreciably in body weight during their period of convalescence. Although the amount of fat as seen in microsections did not approach that seen in alcoholic cirrhosis, it was present to a significant degree. Because the deposition of liver fat is abnormal and possibly harmful, a clinical study of these cases was undertaken.

More than 350 liver biopsies have been performed here during the past three years on soldiers with infectious hepatitis evacuated from Korea to Japan. Deschamps and Steer [1] have reported information gained from the first 84 biopsies of this series. The data presented in this article include 48 of the early biopsies plus 151 subsequent examinations. Patients were studied (1) during the acute phase of hepatitis, while receiving therapeutic agents, or (2) at a later period in the persistent stage, to determine the nature of the complication. Fat accumulation commonly occurred in the subacute and chronic phases but never in the early acute phase of infectious hepatitis.

Methods

Clinical Material: Patients with viral hepatitis were grouped according to the stage of their disease.

1. *Acute Hepatitis:* Seventy-eight serial biopsies were performed on 39 enlisted men during the acute phase of the infection for the purpose of evaluating the effect of vitamin B_{12} on the period of convalescence.[2] All patients had had symptoms of acute uncomplicated hepatitis with jaundice (initial total serum bilirubin of 3.0 mg. per cent or more) for from one to two weeks. They were subjected to liver biopsy within a few days of admission to the hospital, and again at the end of four weeks. One-half received vitamin B_{12} † in a dosage of 1 c.c. (30μg.) every other day for

* Received for publication January 5, 1954.
From the U. S. Army Hospital, Kyoto, Japan. (Present address: V.A. Research Hospital, 333 E. Huron St., Chicago 11, Ill.)

† Normocytin, Lederle.

three doses during their first week of hospitalization, and one-half received no medication. Further methods and treatment are discussed below.

2. *Persistent Hepatitis:* A single biopsy was performed on each of 89 patients having uncomplicated persistent hepatitis, i.e., disease lingering beyond the usual six weeks of convalescence. The reasons for which these biopsies were performed are given in table 1. In most cases there was a continued increase in the percentage of bromsulphalein retained, or enlargement of the liver. Chronic jaundice or symptomatic complaints were present in a smaller number. All of these patients exhibited the typical symptoms and signs of hepatitis, evidence of impairment of liver function by laboratory tests, and the characteristic microscopic findings on biopsy. The liver biopsies were performed at various times (six to 28 weeks; average, 12 to 13 weeks) following the onset of symptoms of hepatitis. Patients having serum hepatitis, infectious mononucleosis, amebiasis, yellow atrophy, portal cirrhosis, hemolytic jaundice or malaria were excluded from the study. However, it is realized that some cases of serum hepatitis may have been

TABLE 1

Indications for Liver Biopsy in Persistent Viral Hepatitis

	Impaired Bromsulphalein Excretion	Enlarged Liver	Jaundice	Continuing Symptoms (Diagnostic)	Total No. of Biopsies
Non-fatty livers	24	15	9	5	53
Fatty livers	21	10	3	2	36
					89

included, since the incidence of parenteral injections within the six months prior to illness was undoubtedly high in these service personnel. Fifteen patients in this series were treated with vitamin B_{12} at some time during their hospital stay, in a dosage of 1 c.c. (30 μg.) every other day for from five to 10 days. Other treatment was as described below.

General: The degree of severity of symptoms before and after entering the hospital was graded once or twice weekly, 0 to 4 plus. Alcohol consumption within the six months prior to illness was estimated (0 to 3 plus).[3] Patients of both groups were confined to their beds except for trips to the bathroom. In determining liver function, the total serum bilirubin [4] and bromsulphalein retention * tests were used, because they are accepted as criteria for ambulation by most investigators. When the serum bilirubin (less than 1.5 mg. per cent) and degree of bromsulphalein retention (5 per cent or less) became normal on biweekly estimations, activity of the patient was gradually increased to normal. Other liver function tests were performed, but will not be included in the present data.

Diet: In general, the diet given all patients, in both the acute and per-

* Dye retention was determined 45 minutes following the injection of 5 mg. bromsulphalein per kilogram of body weight.

sistent stages of the disease, was the same. They were offered a high-protein, high-carbohydrate, high-caloric diet ad libitum, and encouraged to take interval feedings and second helpings. After the first few days in the hospital, patients usually regained their appetites and consumed large amounts of food. The dietary intake was not measured at that time, but this was done later in patients on a similar diet, for the purposes of a fat balance study.[5] The food eaten daily contained some 4,000 to 5,000 calories, with 70 to 150 gm. of protein, 400 to 450 gm. of carbohydrate and 150 to 200 gm. of fat. In spite of attempts at restriction the diet was rela-

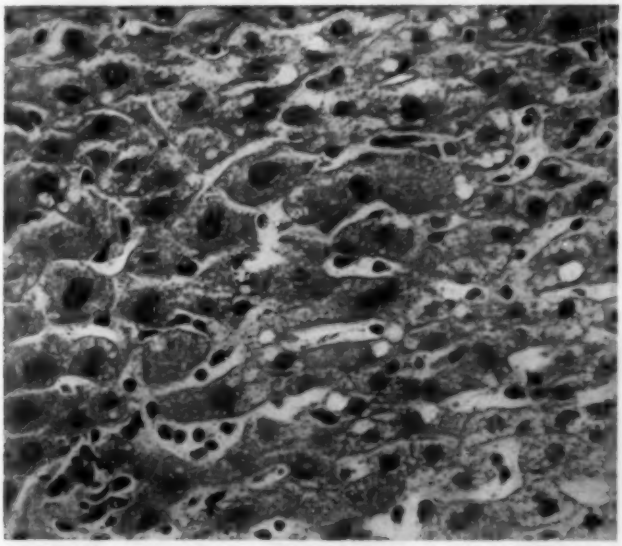


FIG. 1. Section of liver biopsy taken from patient 192 approximately six weeks after the onset of acute infectious hepatitis. This amount of vacuolation, present in scattered, small droplets, is designated as grade 1. H and E, × 350.

tively high in fat, chiefly because of the interval feedings, which contained large amounts of ice-cream.

Biopsies: These were performed by the Vim-Silverman technic,[6] using the intercostal approach through the ninth or tenth interspace. The specimens were fixed in Carnoy's solution, and paraffin sections were prepared by the 406th Medical General Laboratory in Tokyo. These were stained with hematoxylin and eosin and by Masson's method, and Best's carmine stain for glycogen was applied to sections of some of the first specimens obtained. Histochemical tests for fat by Sudan or other methods were excluded by the small size of the specimen.

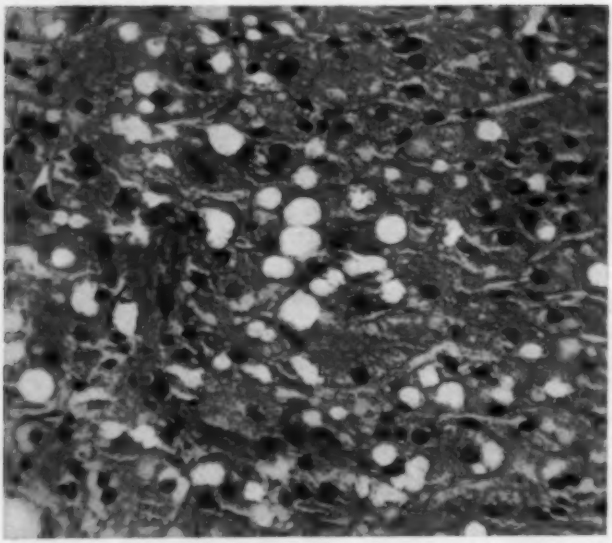


FIG. 2. Liver from patient 126, illustrating the evidence for fat in grade 2 accumulation. H and E, × 350.

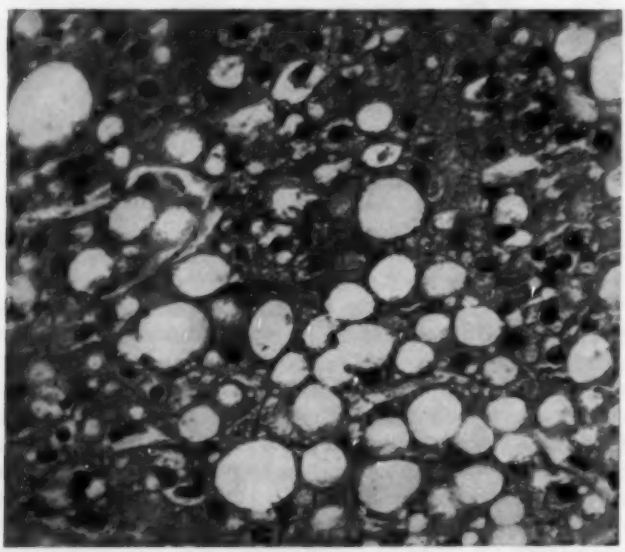


FIG. 3. Liver from the same patient (126). There is fat deposition of grade 3, with large fatty cysts formed by coalescence of several globules. H and E, × 350.

The amount of vacuolation caused by fat observed in each slide was graded, 0 to 4, as follows:

0: No fat or very occasional, tiny droplets.

1: Scattered, small droplets, observed in less than half of the liver cells (figure 1).

2: Medium-sized vacuoles, found in more than half of the cells (figure 2).

3: Larger, diffusely distributed vacuoles, causing displacement of the cell nuclei (figure 3).

Grades 1 to 3 are illustrated in figures 1 to 3. Grade 4 was reserved for the extreme degree of fatty infiltration sometimes found in alcoholic cirrhosis, with the appearance of large fatty cysts, but this grade was absent in any section examined. The amount of condensation reticulinosis was also estimated, using grades of 0, 1 (minimal) and 2 (moderate). Figure 5 illustrates grade 1 reticulinosis. More extensive changes (grades 3 and 4) were not seen. No attempt was made to grade the degree of histologic evidence of inflammatory response. The patients were grouped according to the presence or absence of evidence of liver fat in the paraffin sections.

Results

Acute Hepatitis: Clinical and laboratory data concerning the group of patients with fatty livers following acute infectious hepatitis are presented in table 2. The comparable data on patients without evidence of abnormal hepatic fat are not included here, but average values for both groups are given in table 4. In no case was there evidence of fat in any of the specimens taken by biopsy at the time of admission (about two weeks after the onset of illness). In the biopsies done at four weeks after admission to the hospital, and approximately six weeks after the onset of symptoms of hepatitis, some degree of abnormal fat accumulation in the liver was seen in more than half (54 per cent) of the 39 patients. In most cases there was evidence of a mild degree of accumulation of abnormal fat (grade 1 or 2), and in a few cases it was moderate (grade 3). The average grade of fat was 1.6 (mild). There was no correlation between the amount of abnormal fat present in the liver and the extent of reticulinosis. A minimal degree of fibrosis (grade 1) was seen in more than half of the patients in both groups.

There was a significant difference * in weight gain from time of admission to biopsy, the patients with fatty livers gaining an average of eight pounds as compared with only three pounds in the group without fat. The average age of the patients (23), severity of symptoms (2 plus) and alcohol intake (1 plus) were the same in the two groups. There were more patients showing parasites on stool examination in the group with fatty livers, but this difference is not significant because of the small number. Livers were not enlarged at the time of biopsy in either group. In the subjects who

* The probability that this difference could occur by chance is 0.000674.

TABLE 2

Clinical Data Concerning 21 Patients with Acute Viral Hepatitis Who Exhibited Fatty Livers on Biopsy Performed Six Weeks after Onset

Case No.	Age	Alcohol Intake	Degree of Symptoms	Rx with Vit. B_{12}	Wt. Gain (lbs.)	Liver Size at Biopsy (cm.)	Highest		2nd Biopsy		2nd Biopsy	
							TSB (mg. %)	BSP (%)	TSB (mg. %)	BSP (%)	Fat	Fibrosis
											(grade)	
166	23	++	++	+	13	0	11.9	5	1.1	5	3	1
167	20	++	+	+	7	0	16.0	15	1.7	15	2	1
168	22	++	++++	+	10	0	4.8	10	1.0	5	3	1
169	19	0	++	+	8	0	8.1	7	0.2	5	1	1
171	20	+	++	+	16	0	13.6	25	1.4	10	3	2
178	24	+	+++	+	13	0	14.3	2.5	1.7	2.5	1	1
179	29	0	++	+	5	0	7.6	2.5	2.1	2.5	1	1
180	19	+	++	0	−3	1	14.0	2.5	1.9	2.5	1	1
183	21	++	+++	0	−2	0	5.7	15	1.1	2.5	1	2
184	21	++	++	0	6	0	8.7	10	1.1	2.5	1	1
185	24	+	++	0	4	0	6.4	10	1.9	5	1	1
191	21	0	++	0	13	0	10.5	5	0.5	2.5	2	1
192	20	++	++	0	4	0	23.6	5	1.5	5	2	2
195	24	+	+++	0	9	1	10.7	15	1.1	5	2	1
198	24	+	+++	0	9	0	14.7	10	1.5	10	2	1
202	23	0	+++	+	9	0	3.3	5	0.8	0.5	1	1
204	23	++	+++	+	13	0	8.7	7	1.7	7	1	1
206	23	0	++	0	11	0	2.7	2.5	1.1	2.5	1	1
207	25	+	++	0	17	0	9.0	2.5	1.1	2.5	2	1
210	22	+++	++	+	4	0	15.2	2.5	1.5	2.5	2	1
212	27	0	++	0	11	0	16.8	5	1.1	2.5	2	1
Average of 21 patients												
	23	+	++	(10)	8	0	10.8	7.8	1.3	5	1.6	1

received vitamin B_{12} as a part of their hospital treatment, there was no change in the incidence of hepatic fat. A typical case history on a patient in whom a fatty liver was found at biopsy at six weeks after the onset of hepatitis is presented at the end of this report.

Deposits of fat did not impair liver function demonstrably. The average degree of bromsulphalein retention showed no correlation with the presence of liver fat. Retention was greater both at its highest level (10.0 per cent) and at the time of biopsy (8.1 per cent) in the non-fatty liver group than in the fatty liver group (7.8 per cent and 5.0 per cent). Approximately the same number of subjects in the two groups had abnormal bromsulphalein retention at the time of biopsy. Although one quarter of the patients exhibited a slightly abnormal serum bilirubin (more than 1.5 mg. per cent) at the time of biopsy, the average value was normal in both groups. The severity of the hepatitis, as estimated by the peak of the serum bilirubin, was only slightly greater in patients with fatty livers.

Persistent Hepatitis: Fifty-three (60 per cent) of the 89 biopsies from patients with persistent hepatitis contained no fat on microscopic section. Thirty-six biopsies showed fatty metamorphosis in varying degree, an incidence of 40 per cent. Table 3 presents data regarding patients who de-

veloped fatty livers; values for patients without evidence of abnormal hepatic fat are necessarily omitted because of lack of space. From table 4, it may be seen that the data collected on these two groups may reasonably be compared, since the biopsies were done at about the same time (average, 12 and 13 weeks) after the onset of symptoms. The degree of fatty accumulation averaged grade 1.7 (mild), similar to that found in acute hepatitis. More severe (grade 3) accumulation was seen in only nine cases. The degree of reticulinosis was the same (minimal, grade 1) when associated with fat as when abnormal fat was absent.

TABLE 3

Clinical Data Concerning 36 Patients Who Exhibited Fatty Livers on Biopsy during Persistent Hepatitis

Case No.	Age	Alcohol Intake	Degree of Symptoms	Onset Sympt. to Biopsy (wks.)	Wt. Gain (lbs.)	Liver Size at Biopsy (cm.)	Highest		At Biopsy		At Biopsy	
							TSB (mg. %)	BSP (%)	TSB (mg. %)	BSP (%)	Fat	Fibrosis
											(grade)	
2	20	+	+	6	—	4	0.8	30	0.4	30	1	1
4	18	+	++	6	13	7	3.0	5	0.6	5	3	1
15	20	+	++	8	12	4	3.1	25	1.9	13	1	0
16	30	+	++	8	7	5	0.6	2.5	0.6	2.5	2	2
19	23	0	++	11	32	0	4.2	20	0.3	2.5	3	0
45	22	0	0	10	13	0	23.6	2.5	1.5	2.5	2	0
47	35	—	++++	12	—	4	37.0	5	1.0	2.5	2	1
56	27	++	++	19	—	2	—	—	2.3	2.5	2	0
62	21	+	+++	13	−2	4	4.5	13	2.1	5	2	1
68	30	+	++	14	20	0	5.1	25	1.0	23	1	1
74	30	+++	++	20	24	0	8.1	23	0.8	10	3	2
77	24	—	++	7	—	6	2.5	—	1.0	2.5	1	1
82	31	++	+++	17	27	0	2.5	29	1.9	20	3	0
83	20	0	+	18	—	0	2.8	10	1.9	2.5	2	0
85	35	0	+	17	38	0	14.3	23	0.6	13	1	1
87	20	0	++	9	—	5	5.9	—	1.0	5	1	0
90	22	+	++	16	13	0	6.4	25	1.0	17	1	0
91	19	++	+	20	11	0	6.8	25	1.0	10	1	0
95	21	+	+++	13	18	0	15.1	20	0.8	15	1	1
96	30	++	++	14	31	0	12.5	25	1.0	10	1	1
106	19	+	++	15	14	6	2.3	2.5	0.3	2.5	3	1
110	24	0	+++	8	16	0	11.8	23	1.1	20	1	1
111	19	+	++	15	5	5	1.9	13	1.1	13	1	0
126	21	+	++++	9	21	0	14.0	23	1.5	17	3	0
129	27	++	++	7	9	0	11.8	25	1.5	25	1	1
132	21	+	++	15	14	1	2.7	25	1.0	13	2	1
140	29	+++	++	19	5	0	48.0	25	1.5	25	1	2
152	19	+	+++	16	14	0	10.5	5	3.3	2.5	1	0
211	24	+	++	18	11	0	6.8	15	1.9	13	3	1
219	37	++	++	10	10	0	5.1	25	1.0	10	3	2
223	26	+	++	16	18	0	2.0	20	0.3	10	1	1
227	22	+	++++	6	14	4	8.7	7	1.1	2.5	3	2
228	19	+	++	9	5	4	1.0	10	1.0	10	1	1
229	21	++	++	24	—	6	3.1	2.5	1.0	2.5	1	0
232	24	++	++	13	24	0	13.0	25	1.0	15	2	1
234	22	+	+	8	4	2	5.9	2.5	1.0	2.5	1	0
Average of 36 patients												
	24	+	++	13	16	2	8.1	18.1	1.3	11.2	1.7	1

TABLE 4

Averages of Clinical and Laboratory Findings in Hepatitis Patients with Reference to the Occurrence of Fat in the Liver

	Acute Hepatitis (39 biopsies)		Persistent Hepatitis (89 biopsies)	
	Nonfatty Liver	Fatty Liver	Nonfatty Liver	Fatty Liver
Number (%) of patients	18 (46%)	21 (54%)	53 (60%)	36 (40%)
Average no. weeks from onset of sympt. to biopsy	6	6	12	13
Average age	23	23	24	24
Average degree of severity of symptoms	++	++	++	++
Average alcohol intake	+	+	+	+
No. patients with parasites	1	4	4	4
Average liver enlargement (cm.) at time of biopsy	0	0	2	2
No. patients treated with vitamin B_{12}	10	10	8	7
Average highest TSB during hospitalization (mg. %)	8.0	10.8	7.4	8.1
Average TSB at time of biopsy (mg. %)	1.4	1.3	3.3	1.3
No. (%) patients showing abnormal TSB at biopsy	5 (24%)	6 (29%)	20 (38%)	7 (19%)
Average highest BSP during hospitalization (%)	10.0	7.8	17.9	18.1
Average BSP at time of biopsy (%)	8.1	5.0	12.5	11.2
No. (%) patients showing abnormal BSP at biopsy	6 (33%)	4 (19%)	26 (49%)	21 (58%)
Average wt. gain (lbs.) during hospitalization to time of biopsy	3	8	6	16
Average degree of fat on biopsy	0	1.6	0	1.7
Average degree of reticulinosis	1	1	1	1
No. (%) patients—reticulinosis	11 (61%)	15 (71%)	28 (55%)	23 (64%)

On the average, patients with fatty livers gained far more weight (16 pounds) than did those without abnormal hepatic fat (six pounds) from the time of hospitalization up to the time of biopsy.* The average age (24), degree of severity of symptoms (2 plus), alcohol intake (1 plus) and the presence of parasites (four patients) were the same in the fatty and non-fatty liver groups. Distention with fat did not seem sufficient in these cases to produce an increase in size of the liver, since the average enlargement in both groups was 2 cm. Almost equal numbers of patients in the two groups had been treated with vitamin B_{12} (eight and seven).

The highest average bromsulphalein retention values (18.1 per cent and 17.9 per cent) were the same, regardless of the presence of abnormal hepatic fat. The serum bilirubin in patients with fatty livers was normal (1.3 mg. per cent) at the time of biopsy. On the contrary, patients showing no abnormal fat in their hepatic biopsies were jaundiced at the time of biopsy, their average bilirubin being 3.3 mg. per cent. The average peak of the level of total serum bilirubin was almost the same in the fatty liver group (8.1 mg. per cent) and in the non-fatty liver group (7.4 mg. per cent), indicating a similar degree of severity of hepatitis. A typical case history

* The probability that this difference could occur by chance is 0.000000573.

on a patient showing a fatty liver in association with persistent hepatitis is given later.

Discussion

With few exceptions investigators have stated, in reviewing biopsy and autopsy specimens of patients having acute and chronic infectious hepatitis, that the frequency and degree of fat infiltration is insignificant.[7, 8] Watson [6] pointed out that the absence of fat from the liver in cholangiolitic hepatitis helped to distinguish it pathologically from toxic hepatitis. Mallory [10] noticed that many liver cells contained fat vacuoles in the post-icteric cases, and believed that this was a new finding. Deschamps [1] recognized the frequency of fatty metamorphosis in the early biopsies performed at this hospital on patients with chronic hepatitis (17 per cent of cases). In no discussion of the pathology of infectious hepatitis has an incidence approaching that in this series been reported. The fat was seen in both the subacute and the persistent cases, in approximately the same frequency (54 per cent and 40 per cent) at different stages of the disease. It is suspected that a higher incidence and more extensive degree of fatty change might have been demonstrated if frozen sections could have been stained for fat.[11] The fat was not present at the time of admission (one to two weeks after the onset of symptoms), but appeared at some time before six weeks, and was noted in two fifths of patients with chronic hepatitis of an average of 13 weeks' duration. Although not severe, it appeared in a significant degree (average, minimal to moderate) at both times.

Cause: The association of abnormal hepatic fat with excessive gain in body weight during convalescence from infectious hepatitis was striking. This relation was suspected by Steer [12] during a review of the early biopsies of this series. At both six and 13 weeks after the onset of hepatitis, the patients with fatty livers had gained more than twice as much weight as those with no abnormal fat in their livers. As a rule, these men had lost from five to 20 pounds in weight during their several months of duty in Korea.[5] During treatment in the hospital they were fed a high-caloric, high-protein, high-fat diet, and remained at decreased physical activity for from one to several months. It is likely that under these conditions their caloric output was exceeded by their caloric intake, and that fat therefore accumulated in the liver.

From the data at hand it is impossible to assess the relative importance of the weight gain and hepatitis in producing the fatty change. No biopsies have been obtained on normal patients *without* hepatitis who have shown a similar rapid weight gain, and it is possible that the same change might be found in this situation. Infection may contribute to the inability of the parenchymal cells to metabolize fat. The presence of fat was not related to the previous alcohol intake, although a history of moderate alcoholism was obtained in some cases.

Relation of Jaundice to Liver Fat: It has been shown in this [5] and other

laboratories [13] that intestinal absorption of fat is impaired by deficient bile flow associated with infectious hepatitis with jaundice. The amount of fecal fat excretion is correlated directly with the level of the serum bilirubin. In the present series the presence of jaundice actually seemed to protect against abnormal deposition of fat in the liver. Patients with chronic hepatitis who exhibited fatty livers on biopsy were anicteric (average bilirubin, 1.3 mg. per cent), whereas those who had no abnormal hepatic fat were jaundiced (3.3 mg. per cent). Cantarow [14] described a decrease in histologically visible liver fat during experimental biliary stasis. As the level of total serum bilirubin approaches normal, fat absorption increases, and it is probably after the jaundice has disappeared that fatty deposition occurs in the diseased liver.

Function of Fatty Livers: From the data at hand it would seem that the accumulation of fat in the liver during infectious hepatitis does not impair liver function, as measured by the bromsulphalein retention test. Dye was removed by the fatty liver even more efficiently than by the non-fatty liver, six weeks after the onset of hepatitis. After 12 or 13 weeks there was no difference in this function. However, no attempt was made to compare the duration of disease up to the time of full recovery in the two groups of the chronic series, and it is possible that patients with fatty accumulation in their livers exhibited a longer course of hepatitis.

From other studies of liver function as affected by the experimental production of fat deposition,[15, 16, 17] it may be concluded that the accumulation of fat to a marked degree does impair function. The bromsulphalein test is probably the most sensitive and specific test known at present for measuring this abnormality. Clinical data support evidence found by animal studies.[18] The amount of fat noted in infectious hepatitis does not approach that found in alcoholic cirrhosis (grade 4). It cannot be said that this excess fat is harmful, but its presence in histologically visible amount is abnormal.

Predisposition of Fatty Metamorphosis to Fibrosis: The possible rôle of infectious hepatitis in the etiology of portal cirrhosis has received recent attention.[19, 20] The present data contribute little to this problem, except to emphasize the frequency of abnormal hepatic fat accumulation following hepatitis in patients who have recently gained weight rapidly. It has been postulated that marked fat deposition may predispose to cirrhosis, by means of compression of parenchymal cells and sinusoids, with resulting ischemic necrosis and fibrosis.[21, 22] Hartroft [23] believes that rupture of liver cells from an excess of fat accumulation results in fibrosis. Appearance of fibrous tissue occurs, coincidental with the removal of fat from the parenchymal cells. A longer period of observation with serial biopsies on patients with fatty livers following hepatitis is necessary in order to investigate this. In a few patients who have had several biopsies to determine the course of the fatty change as affected by therapy, there has been no significant appearance of scar tissue.

The degree of reticulinosis in our sections was the same in the livers containing fat as in those without fat, in both the acute and persistent groups. A minimal grade of fibrosis (figure 5) was present in somewhat more than half of the cases at six and 12 weeks after the onset of hepatitis. The fat seen in most slides had a pericentral location (figure 4), whereas the fibrous tissue was periportal in distribution (figure 5). It may therefore be suspected that there is no causative association between these two elements.

Dietary Treatment: In our patients, abnormal hepatic fat accumulation seemed to be associated with excessive gain in body weight during the treatment of infectious hepatitis. Hepatic function was not demonstrably impaired by this condition, and it did not result in cirrhosis of the liver. However, this abnormal deposition of fat should be prevented by restriction of caloric intake and, therefore, of dietary fat. Some authors [24, 25] have recently indicated that, to insure that food is palatable, the fat intake should not be limited in the treatment of liver disease, and it is a widely accepted belief that feeding of unlimited amounts of calories is mandatory. Our findings suggest that, in the therapy of infectious hepatitis, the dietary fat should be restricted to approximately 100 gm. Body weight should be checked periodically, at least twice a week, and maintained at a fairly constant level. Any tendency toward obesity should be curbed.

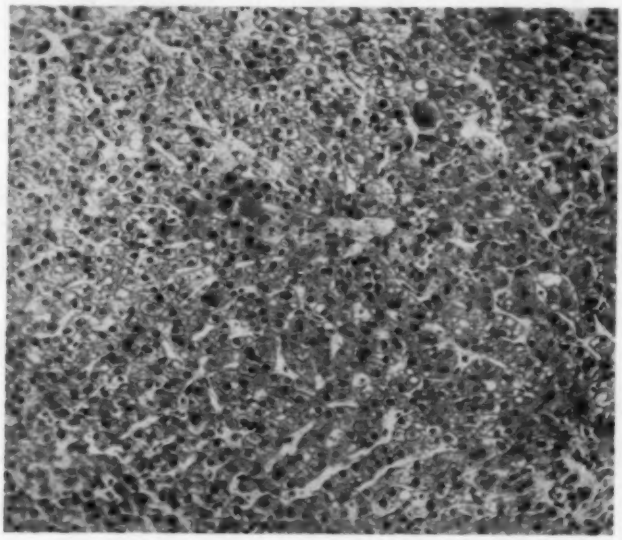


FIG. 4. This section from patient 192 shows the characteristic distribution of small fat droplets around the central vein in a patient convalescing from infectious hepatitis. H and E, × 125.

Best and associates [26] have emphasized that liver fat will not appear in the experimental animal unless the caloric intake is generous. Fatty livers of this type may be caused by low dietary protein, deficient in relation to the large number of calories ingested. It has been recently proved by a hepatitis research team working at this hospital [27] that an increased food intake, particularly in the form of protein, will shorten the period of convalescence from hepatitis. A high-protein diet necessarily contains a moderate amount of fat, but it is felt that the latter element should be reasonably limited.

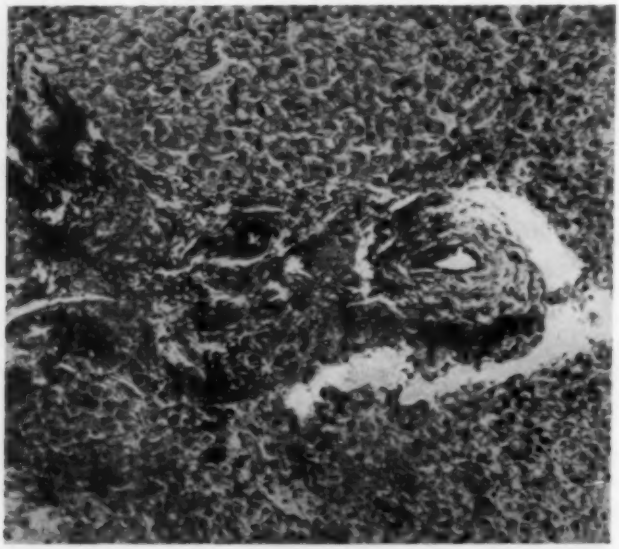


FIG. 5. Liver tissue from the same patient (192) shows mild reticulinosis (grade 1) in the portal area. H and E, × 125.

Treatment with Lipotropic Agents: Campbell [28] originally believed that administration of vitamin B_{12} shortened the period of convalescence in hepatitis patients, but this finding was not confirmed in patients with acute disease in the present series.[2] A third study was performed, using a longer period of administration of the drug (table 5), in order to determine the possible lipotropic effect of the drug on the fatty liver of infectious hepatitis. Eight patients with acute hepatitis were given vitamin B_{12} * in a dosage of 0.5 c.c. (15 μg.) every other day for four weeks, and a placebo † was given to eight control subjects. Choice of the drug was randomized, so that its identity remained unknown to the patient and the investigator. Liver

* Normocytin, Lederle.

† A solution of a few drops of Safronin dye was made up to resemble vitamin B_{12} in color, and placed in empty Normocytin vials.

biopsies were performed within two or three days of admission to the hospital and again in four weeks. Results (table 5) show that the incidence of liver fat seen on biopsy section after four weeks of illness was the same in the two groups. No fat was seen on any biopsy taken on admission. The data for experimental and control groups are not ideally comparable, since the former group exhibited a more severe hepatitis (average bilirubin, 10.5 mg. per cent) than the latter (6.6 mg. per cent). However, the duration of illness did not seem to be affected by the administration of vitamin B_{12}.

TABLE 5

Failure of Vitamin B_{12} to Prevent Accumulation of Liver Fat in Patients with Acute Viral Hepatitis

Case No.	Time to Ambulation (days)	Initial TSB (mg. %)	Wt. Gain (lbs.)	Liver Fat (grade)
		Vitamin B_{12} Group		
290	20	10.2	10	1
291	23	9.9	6	2
292	27	13.6	7	3
294	24	6.6	10	1
297	24	7.9	9	2
306	26	12.5	15	0
320	24	12.0	11	2
331	18	11.4	8	0
Average	23	10.5	9	1
		Placebo Group		
284	32	8.0	13	1
285	19	4.5	5	1
296	29	9.0	7	2
316	24	7.6	7	1
321	22	7.3	4	1
327	24	3.4	10	2
328	11	4.8	6	1
332	12	8.1	6	1
Average	22	6.6	7	1

It is concluded that vitamin B_{12} will not prevent the abnormal accumulation of fat in the liver of patients with infectious hepatitis. This compound has lipotropic activity in the experimental animal.[29, 30, 31, 32] In the human, it may cause excessive weight gain by increasing appetite, and should not be used in hepatitis unless the patient has anorexia. It is suspected that Aureomycin [33] and cortisone [34] may cause abnormal accumulation of hepatic fat, and therefore may also be harmful in the therapy of infectious hepatitis. No data have been collected at this hospital regarding the lipotropic effect of choline in this disease. It is the impression here and elsewhere [35] that its administration may aid in the disappearance of

stainable fat from some diseased livers, but this finding is doubtful and variable in the case of infectious hepatitis.[36, 37]

Summary

A significant degree of accumulation of abnormal hepatic fat was demonstrated by needle biopsy to occur in approximately one-half of 144 soldiers with infectious hepatitis, at an average of six and 13 weeks after the onset of symptoms. Clinical, laboratory and pathologic data regarding patients with fatty livers were compared with values for those showing no fat. At both the acute (six weeks) and persistent (13 weeks) phases of the disease, gain of body weight in patients with fatty livers was more than twice that in those without hepatic fat. It is concluded that increased caloric intake, and, necessarily, intake of fat, perhaps associated with a "relative protein deficiency," were responsible for the fat deposition. Hepatic function, as estimated by the bromsulphalein retention test, was not impaired by the accumulation of fat, and the incidence of reticulinosis was no greater when abnormal hepatic fat was present. Although it is impossible to state whether this fat is harmful, its presence on histologic section is abnormal. Therefore, the dietary fat and caloric intake should be moderately limited, so that obesity does not occur. Vitamin B_{12} had no lipotropic effect in this condition, but its use might be justified to increase the appetite in anorectic patients.

Case Reports

Case 1. Acute Hepatitis. Case 115. This 23 year old corporal, a member of the military police, in Seoul, Korea, was admitted to the hospital on July 10, 1951. On June 30 he had awakened with a stiff neck, headache and slight fever. Appetite became poor, and he felt weak and listless. There was no abdominal pain, vomiting or diarrhea. On July 3 the urine turned dark in color, and the following day he reported on sick-call. A urine test for bile on July 7 was positive, so he was evacuated to Japan. Past history was significant in that the patient had been treated in Japan in 1947 for a bout of infectious hepatitis. He had been given smallpox and typhus injections for immunization four months prior to admission, and injections against cholera and Japanese B encephalitis two months before. There was a history of moderate intake of alcohol.

On physical examination the patient showed 2 plus jaundice of skin and sclerae, a few spider angiomata, and mild tenderness in the right upper quadrant of the abdomen. The liver was not palpable. The total serum bilirubin on July 12 was 11.9 mg. per cent. Blood counts, serologic tests for syphilis, stools, urinalysis and chest x-ray were normal. The patient complained of anorexia and malaise, which subsided within one week. He was kept at bed-rest and fed a high-protein, high-caloric diet. During the first week three injections of 30 μg. of vitamin B_{12} were administered. By August 9 the total serum bilirubin and bromsulphalein retention were within normal limits, so the patient was permitted to resume normal activity. Body weight on admission was 160 pounds, and by August 9 he had gained 13 pounds.

A liver biopsy performed on July 12 showed a moderately severe active hepatitis, with marked destruction of liver cells in certain areas, focal necrosis and infiltration of polymorphonuclear leukocytes and lymphocytes. There was no evidence of fatty

metamorphosis. The patient was again subjected to a liver biopsy on August 7, which revealed minimal residual activity with definite healing. There was minimal reticulinosis in an occasional portal area, and small areas of cellular infiltration were seen. A moderate degree of fatty vacuolation of parenchymal cells was now apparent. The patient's liver function tests remained normal after two weeks with pass privileges, and he was then discharged to full duty, since the results of the second biopsy were as yet unknown.

Case 2. Persistent Hepatitis. Case 126. This 21 year old private in the Quartermaster Corps was admitted to the hospital on May 16, 1951, after several months of duty in Pusan, Korea. On May 8 he vomited upon arising, and became progressively weak and tired. He developed anorexia, fever, muscular aches, headaches

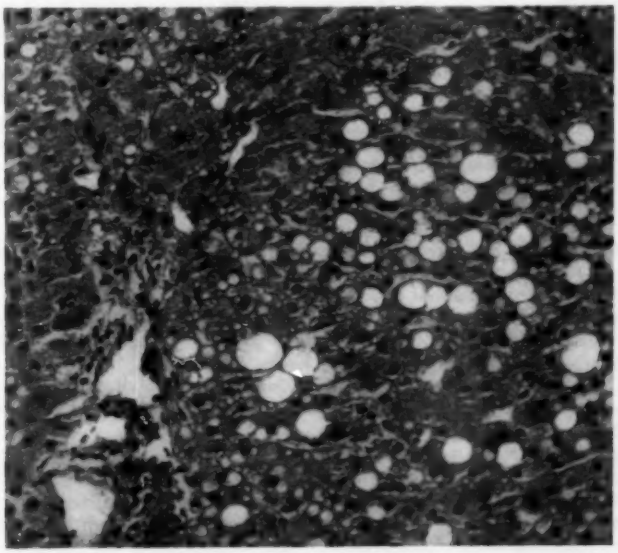


FIG. 6. A section of liver biopsy from case 126 reveals the accumulation of diffuse fat vacuoles, with minimal fibrosis. Before the liver biopsy was done this patient had gained 21 pounds in body weight during nine weeks of treatment for infectious hepatitis with jaundice (see case report). H and E, × 240.

and fatigue on May 9. Urine became dark on May 10, and he continued to vomit several times daily. He noticed jaundice the following day and reported on sick-call. During the course of his evacuation from Korea to Japan he developed diarrhea, and passed as many as 16 loose, watery bowel movements per day, containing no gross blood. He had been immunized against smallpox, typhus, typhoid fever, tetanus, cholera and influenza two months before hospitalization. There was a history of minimal intake of alcohol, restricted to several bottles of beer per week. Past history was otherwise noncontributory.

Physical examination was negative except for moderate icterus of skin and sclerae, and a tender liver extending 2 cm. below the costal margin. Total serum bilirubin on admission was 14.0 mg. per cent. Blood counts, urinalysis, serology and chest x-ray were normal. The patient was treated with a high-protein, high-

caloric diet at bed-rest. Within a week his anorexia, vomiting and malaise had subsided, and his bilirubin dropped to 3.3 mg. per cent. Stools showed ascaris ova, so he was treated with hexylresorcinol. On July 19, because of a prolonged convalescence and a persistently elevated bromsulphalein dye test (23 per cent), he was subjected to a liver biopsy. By this time he had gained 21 pounds in weight, from 158 to 179, and the total serum bilirubin was 1.5 mg. per cent. Sections showed a moderately severe fatty vacuolation of parenchymal cells of the liver (grade 3, figure 6). Following the biopsy the patient was given a course of choline, and his bilirubin and bromsulphalein retention became normal on August 2. He was allowed gradually increasing ambulation, and was discharged on August 16 when laboratory tests remained normal.

ACKNOWLEDGMENTS

The author wishes to express his appreciation to the following officers of the United States Army for their assistance in completing this project: Colonel Francis W. Pruitt, Colonel Charles L. Leedham, Colonel Sterrett E. Dietrich, Colonel Roger H. Albee, Lt. Colonel Robert Jordan, Lt. Colonel Arthur Steer, Major Robert E. Campbell and Captain Stephen H. Deschamps. Dr. Thomas C. Chalmers, Dr. Charles Davidson and the other members of the hepatitis research team, U. S. Army Hospital, Kyoto, Japan, offered inspiration and advice. Dr. W. Stanley Hartroft, Professor in the Banting and Best Department of Medical Research, University of Toronto, kindly reviewed the manuscript and prepared the photomicrographs.

BIBLIOGRAPHY

1. Deschamps, S. H., and Steer, A.: Experience with needle liver biopsies at the hepatitis center for Japan and Korea, 1950–51, Am. J. Med. **6**: 72, 1948.
2. Campbell, R. E.: Unpublished data.
3. Chalmers, T. C., Eckhardt, R. D., Reynolds, W. E., Cigarroa, J. G., Deane, N., Reifenstein, R. W., and Smith, C. W.: Protocol for study of the treatment of infectious hepatitis at the U. S. Army Hospital, Kyoto, Japan, p. 20.
4. Ducci, H., and Watson, C. J.: Quantitative determination of the serum bilirubin with special reference to the prompt reacting and the chloroform soluble types, J. Lab. and Clin. Med. **30**: 293, 1945.
5. Colwell, A. R., Jr.: Unpublished paper.
6. Iverson, P., and Roholm, K.: Aspiration biopsy of the liver, with remarks on its diagnostic significance, Acta med. Scandinav. **102**: 1, 1939.
7. Popper, H., and Franklin, M.: Diagnosis of hepatitis by histologic and functional laboratory methods, J. A. M. A. **137**: 230, 1948.
8. Sborov, V. M., and Keller, T. C.: The diagnosis of hepatitis, Gastroenterology **19**: 424, 1951.
9. Watson, C. J., and Hoffbauer, F. W.: The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver, Ann. Int. Med. **25**: 195, 1946.
10. Mallory, T. B.: Pathology of epidemic hepatitis, J. A. M. A. **134**: 645, 1947.
11. Hartroft, W. S.: Personal communication.
12. Steer, A.: Professional Section, Annual Historical Report, 406 Medical General Laboratory, U. S. Army, Tokyo, Japan, p. 103.
13. Gross, J. B., Comfort, M. W., Wollaeger, E. E., and Power, M. H.: Total solids, fat and nitrogen in the feces: V. A study of patients with primary parenchymatous hepatic disease, Gastroenterology **16**: 140, 1950.
14. Cantarow, A.: Biliary stasis and decompression. A review of recent contributions, Internat. Clin. **1**: 272, 1938.
15. MacLean, D. L., Ridout, J. H., and Best, C. H.: The effects of diets low in choline upon liver function, growth and distribution of fat in the white rat, Brit. J. Exper. Path. **18**: 345, 1937.

16. McKibbin, J. M., Thayer, S., and Stare, F. J.: Choline deficiency studies in dogs, J. Lab. and Clin. Med. **29**: 1109, 1944.
17. Koch-weser, D., Farber, E., and Popper, H.: Fatty liver with and without necrosis, Arch. Path. **51**: 498, 1951.
18. Ulevitch, H., Gall, E. A., Abernathy, E. L., and Schiff, L.: Needle biopsy of the liver. VII. Observations in fatty vacuolization of the liver, Gastroenterology **18**: 1, 1951.
19. Howard, R., and Watson, C. J.: Antecedent jaundice in cirrhosis of the liver, Arch. Int. Med. **80**: 1, 1947.
20. Cayer, D., and Cornatzer, W. E.: The effects of lipotropic factors on the phospholipide turnover in patients with infectious hepatitis, Gastroenterology **18**: 79, 1951.
21. Karsner, H. T.: Morphology and pathogenesis of hepatic cirrhosis, Am. J. Clin. Path. **13**: 569, 1943.
22. Gyorgy, P.: Nutritional aspects of liver injury, M. Clin. North America **33**: 1657 (Nov.) 1949.
23. Hartroft, W. S.: Accumulation of fat in liver cells and in lipodiastaemata preceding experimental dietary cirrhosis, Anat. Rec. **106**: 61, 1950.
24. Volwiler, W., Jones, C. M., and Mallory, T. B.: Criteria for the measurement of results of treatment in fatty cirrhosis, Gastroenterology **11**: 164, 1948.
25. Popper, H., Steigmann, F., Meyer, K. A., Kozoll, D. D., and Franklin, M.: Correlation of liver function and liver structure, clinical applications, Am. J. Med. **6**: 278, 1949.
26. Best, C. H., Hartroft, W. S., Lucas, C. C., and Ridout, J. H.: Liver damage produced by feeding alcohol or sugar and its prevention by choline, Brit. M. J. **2**: 1001, 1949.
27. Chalmers, T. C., Davidson, C., Eckhardt, R. D., Reynolds, W. E., Cigarroa, J. G., Deane, N., Reifenstein, R. W., and Smith, C. W.: Unpublished paper.
28. Campbell, R. E., and Pruitt, F. W.: Vitamin B_{12} in the treatment of viral hepatitis, Am. J. M. Sc. **224**: 252, 1952.
29. Bennett, M. A., Joralemon, J., and Halpern, P. E.: The effect of vitamin B_{12} on rat growth and fat infiltration of the liver, J. Biol. Chem. **193**: 285, 1950.
30. Cartwright, G. E., Tatting, B., Robinson, J., Fellows, N. M., Gunn, F. D., and Wintrobe, M. M.: Hematologic manifestations of vitamin B_{12} deficiency in swine, Blood **6**: 867, 1951.
31. Koch-weser, D., and Popper, H.: Correlation between ribose nucleic acid depletion and other signs of liver damage as influenced by vitamin B_{12}, J. Lab. and Clin. Med. **34**: 1764, 1950.
32. Gyorgy, P., and Rose, C. S.: Effect of vitamin B_{12} on experimental liver injury, Proc. Soc. Exper. Biol. and Med. **73**: 372, 1950.
33. Sborov, V. M., and Sutherland, D. A.: Fatty liver following Aureomycin and Terramycin therapy in chronic hepatic disease, Gastroenterology **18**: 598, 1951.
34. Evans, A. S., Sprinz, H., and Nelson, R. S.: Adrenal hormone therapy in viral hepatitis. II. The effect of cortisone in the acute disease, Ann. Int. Med. **38**: 1134, 1953.
35. Franklin, M., Salk, M. R., Steigmann, F., and Popper, H.: Clinical, functional and histological responses of fatty metamorphosis of human liver to lipotropic therapy, Am. J. Clin. Path. **18**: 273, 1948.
36. Kinsell, L. W., Michaels, G. D., Barton, H. L., and Weiss, H. A.: Protein balance studies in patients with liver damage. II. The role of lipotropic agents, Ann. Int. Med. **29**: 881, 1948.
37. Cayer, D., and Cornatzer, W. E.: The use of lipotropic factors in the treatment of liver disease, Gastroenterology **20**: 385, 1952.

PULMONARY FUNCTION IN MITRAL STENOSIS: A REVIEW OF CURRENT CONCEPTS *

By Ralph C. Scott, M.D., *Cincinnati, Ohio*

It is a well known fact that patients with mitral stenosis are frequently troubled with dyspnea. The dyspnea may be minimal and present only on exertion in milder cases of stenosis, or it may be extreme and incapacitating in cases of more severe stenosis. The dyspnea and diminished vital capacity may be related to the pulmonary congestion and hypertension so common in these patients. When the pressure in the pulmonary capillaries exceeds the colloid osmotic pressure of plasma, the patients are in danger of developing pulmonary edema. Alteration in the alveolar-capillary membrane also may be important in the pulmonary symptoms experienced by these patients. In recent years and with modern tools numerous workers have carried out careful studies to explore the respiratory dysfunction of mitral stenosis. The present article attempts to bring together the results of these studies and to review the current concepts of the disturbed physiology.

Exertional Dyspnea

Lewis and associates [1] found that their five patients with mitral stenosis who had minimal dyspnea had neither severe stenosis (valve areas ranging from 1.3 to 2.5 cm.^{2}) nor significant elevation of pulmonary arteriolar resistance (all values less than 145 dynes seconds cm.$^{-5}$). They found that dyspnea was disabling in 13 patients whose valve areas were smaller (0.5 to 1.1 cm.^{2}) but whose arteriolar resistance was only slightly elevated (150 to 569 dynes seconds cm.$^{-5}$). These patients were unable to perform even light work. On the other hand, these same workers had five patients who had severe stenosis (0.5 to 0.7 cm.^{2}), together with moderate elevations of pulmonary arteriolar resistance (488 to 853 dynes seconds cm.$^{-5}$), and yet were not incapacitated by dyspnea. Finally, they had seven patients with severe stenosis in whom further elevation of pulmonary arteriolar resistance to levels ranging from 711 to 1662 dynes seconds cm.$^{-5}$ was accompanied by disabling dyspnea.

Borden and associates [2] found in their study of 31 patients with mitral stenosis that there was a rough linear correlation between pulmonary artery pressures and functional capacity as expressed by the criteria of the New York Heart Association. In their 17 patients who were asymptomatic or only slightly incapacitated by dyspnea (Classes I and II), the average pulmonary systolic pressure was 30 mm. Hg and the diastolic 16 mm. Hg.

* Received for publication March 12, 1954.

From the Cardiac Laboratory, Cincinnati General Hospital, and the Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio.

Their 14 patients who were partly or completely incapacitated by exertional dyspnea (Classes III and IV) had an average pulmonary systolic pressure of 69 mm. Hg and a diastolic pressure of 34 mm. Hg.

Ferrer and associates [3] found in their study of 16 cases of mitral stenosis that the 10 who had symptoms on exertion showed pulmonary hypertension at rest. Cardiac output at rest was low in all but two cases. Five of the 16 patients with mitral stenosis had dyspnea at rest. Severe pulmonary hypertension (33 to 81 mm. Hg mean pressure) was found in all five. Cardiac output was normal in two, and very low in three. They exercised four in the first group (symptomatic only on exertion) and three in the second group (symptomatic at rest), and found that preëxisting pulmonary hypertension was always aggravated even in the absence of increase in cardiac output. They digitalized two of these patients and concluded that in one case the pulmonary hypertension was due to left ventricular failure and in the other to block at the mitral valve.

Ellis and his group [4] found a definite correlation between the degree of pulmonary symptoms and the height of the pulmonary artery pressure. This correlation was even more apparent during exercise. These workers also found that two of their patients who had markedly elevated pulmonary arteriolar resistances (870 and 740 dynes sec. cm.$^{-5}$) were seriously incapacitated by dyspnea, but were not subject to acute pulmonary edema. These findings are in agreement with those of Lewis and co-workers.[1]

Ellis et al.[4] found poor correlation between arterial oxygen saturation and the degree of pulmonary dysfunction. Regardless of the degree of dyspnea in most of their patients, the resting saturation was only slightly below 95 per cent and improved with exercise. In eight patients it fell below 90 per cent; chronic dyspnea was severe in seven of these cases. On the other hand, in numerous other cases in their series with severe dyspnea, the arterial oxygen saturation was essentially normal.

Carroll, Cohn and Riley [11b] studied 29 patients with mitral stenosis. They showed that dyspnea correlated well with physiologic abnormalities, being minimal or absent in those with normal respiratory function and severe in those with evidence of impaired diffusion of oxygen and abnormalities of distribution of blood and gas to the alveoli. These workers state that dyspnea has long been considered a manifestation of pulmonary congestion which, they point out, contributes to abnormalities of distribution.

Pulmonary Edema

Draper and associates [5] found in their study of 18 cases of mitral stenosis that the 10 patients who gave a history of pulmonary edema had pulmonary "capillary" pressures averaging 36.3 mm. Hg at rest and 43.5 mm. Hg on exercise. In the patients who did not have a history of pulmonary edema, the average pulmonary "capillary" pressure was lower, being 23.1 mm. Hg at rest and 27.5 mm. Hg on exercise.

Gorlin et al.[6] found that six of 21 patients with mitral stenosis studied had pulmonary edema at rest. Each of these had pulmonary "capillary" pressures greater than 30 mm. Hg. Five of their six patients had abnormally low arterial oxygen saturations, ranging from 80 per cent to 92 per cent. This was taken to indicate interference with diffusion of oxygen. They found two other patients, who had extreme elevations of pulmonary arteriolar resistance (950 and 1480 dynes sec. cm.$^{-5}$) and no clinical evidence of pulmonary edema, to have arterial oxygen saturations of 85 per cent and 90 per cent, respectively. In these two cases it was suggested that the unsaturation was due to pulmonary parenchymal disease, preventing normal oxygen diffusion between alveoli and capillaries.

In three patients whose resting pulmonary "capillary" pressures were elevated (26 to 33 mm. Hg), these same workers [6] also showed that pulmonary edema occurred during three minutes of exercise. These patients had some orthopnea at rest, interpreted to indicate the presence of some pulmonary congestion even before exercise. On the other hand, they had three other patients whose resting pulmonary "capillary" pressures were less than 25 mm. Hg, who had extreme elevation of pulmonary "capillary" pressure after three minutes of exercise (41 to 46 mm. Hg), and yet did not develop pulmonary edema. They pointed out that whether pulmonary edema develops probably depends upon a number of factors such as duration of pressure elevation above the colloid osmotic pressure of plasma, the occurrence of thickened alveolar basement membranes, the height of the hydrostatic pressure gradient, the rate of transudation at a given gradient, etc.

Ellis and associates,[4] in their study of 38 patients with mitral stenosis, encountered 11 who were subject to severe bouts of acute pulmonary edema. Ten of the 11 were in normal sinus rhythm, and had good cardiac output which could frequently be increased with exercise. (Precipitating factors which resulted in attacks of pulmonary edema in these patients were infections of the upper respiratory tract, premenstrual fluid retention, exercise, excitement.) One patient who had severe bouts of acute pulmonary edema had only moderately elevated pulmonary "capillary" pressure and pulmonary arteriolar resistance and a competent right ventricle. Ultimately he developed right-sided failure and the pulmonary arteriolar resistance was found to be considerably increased.

Araujo and Lukas [7] found in their study that the resting pulmonary "capillary" pressures in the 34 cases of mitral stenosis where initial valve areas were below 1.4 cm.^{2} ranged from 21 to 36 mm. Hg, with a mean of 28 mm. Hg. Despite the fact that this pressure was in the range of the colloid osmotic pressure of plasma (25 to 30 mm. Hg), no significant pulmonary edema occurred in any of these cases. With exercise the pulmonary "capillary" pressure exceeded plasma colloid osmotic pressure, yet pulmonary edema occurred in only one patient. In this patient the pulmonary "capillary" pressure was 54 mm. Hg. These authors attribute the failure to develop pulmonary edema to changes in the permeability of the alveolar-

capillary membrane such as capillary basement membrane thickening or pericapillary fibrosis.

These same workers also found no evidence that pulmonary arteriolar constriction occurs when the pulmonary "capillary" pressure equals that of the osmotic pressure of plasma.

Paroxysmal Nocturnal Dyspnea

Lewis and co-workers [3] divided their 16 patients with mitral stenosis who suffered from paroxysmal nocturnal dyspnea into two groups, based upon the level of the pulmonary arteriolar resistances. The one group (nine patients) had narrow mitral valves (0.5 to 1.1 $cm.^2$) and only slight increases in arteriolar resistance (150 to 569 dynes seconds $cm.^{-5}$). They could readily increase their cardiac output in response to stimuli such as increased blood volume during sleep and thus engorge the pulmonary bed. The other group had severe mitral stenosis (six patients with a mitral valve less than 1.0 $cm.^2$ and one patient with a mitral valve of 1.4 $cm.^2$) and marked elevation of pulmonary arteriolar resistance (711 to 1660 dynes seconds $cm.^{-5}$). This second group had dilated hearts and were unable to increase cardiac output. However, as Lewis, Gorlin and associates [1, 8] pointed out, changes in position or tachycardia can result in elevated pulmonary "capillary" pressures and pulmonary edema. This was the probable mechanism of the development of pulmonary edema in this second group.

Ventilatory Function Tests

Borden and associates [2] studied the correlation between pulmonary artery pressure and vital capacity in mitral stenosis. They found it to be less striking than had been anticipated, but noted that patients with moderate to marked pulmonary arterial hypertension all had decreased vital capacities. On the other hand, they found some patients with severe reduction in vital capacity but no marked elevation in pulmonary artery pressure.

Frank, Cugell, Gaensler and Ellis [5] measured vital capacity (both total and timed), maximal breathing capacity, residual volume, inspiratory capacity, expiratory reserve, intrapulmonary mixing, and breathing reserve in 62 patients with mitral stenosis. In those patients who were asymptomatic all measurements of pulmonary function during both rest and exercise were normal. As disability increased there was progressive reduction in maximal breathing capacity, and total and timed vital capacity. Reductions in inspiratory capacity and expiratory reserve volume were symmetrical throughout all stages of disability. They found in cases of severe disability that the total lung capacity was decreased chiefly at the expense of the vital capacity. Though the residual volume increased relatively, there was no defect in intrapulmonary mixing. Breathing reserve was not seriously depleted until disability was marked. These workers found that patients

with slight limitation of activity were uncomfortable during walking exercise but did not hyperventilate. They found that cases of mitral stenosis before the onset of congestive failure are disabled out of proportion to the measured defects in ventilatory function, in contrast to those with pulmonary disease. These workers postulated two mechanisms occurring in patients with mitral stenosis. Early pulmonary hypertension reduces lung compliance elasticity and interferes with maximal flow velocity. Later, as congestive failure ensues and blood volume increases, the total lung capacity is reduced.

Alveolar-Arterial Oxygen Tension Gradient

Blount, McCord and Anderson [10] measured the mean arterial oxygen tension in 18 patients with mitral stenosis at rest and found it to be 66.3 mm. Hg ± 1.67. (Normal for their laboratory is 74.8 mm. Hg ± 1.27.) The mean alveolar oxygen tension was calculated in these same 18 patients at rest and found to be 77.9 mm. Hg ± 2.10. (Normal for their laboratory is 79.6 mm. Hg ± 1.97.) The mean alveolar-arterial oxygen tension gradient at rest was therefore found to be 11.6 mm. Hg ± 1.56. (Normal for their laboratory is 4.8 mm. Hg ± 1.06.) These patients were exercised and measurements repeated. The arterial oxygen tension then was found to have a mean value of 68.4 mm. Hg ± 1.84. (Normal mean value in their laboratory with exercise is 75.3 mm. Hg ± 1.23.) The mean value of the alveolar oxygen tension with exercise was 83.9 mm. Hg ± 2.38. (Normal mean value with exercise is 86.0 mm. Hg ± 1.13.) The mean alveolar-arterial oxygen tension gradient with exercise was 15.5 mm. Hg ± 1.40. (Normal mean gradient with exercise is 10.7 mm. Hg ± 1.15.)

These workers thus demonstrated that in cases of mitral stenosis at rest there is a normal alveolar oxygen tension, a decreased arterial oxygen tension and an abnormally increased alveolar-arterial oxygen pressure gradient. With exercise they found the alveolar oxygen tension gradient to increase.

Diffusion and Distribution Characteristics

Carroll and Riley [11a] determined the diffusing capacity of the lungs in 26 patients with mitral stenosis. They found a low diffusing capacity in all cases studied during exercise, indicating impaired capillary function. They found that the mean pulmonary artery pressure and pulmonary resistance are inversely related to the diffusing capacity. In general, the degree of impairment of diffusion correlated well with the severity of exertional dyspnea. These workers also studied the distribution of circulation and ventilation throughout the lungs. They found that abnormalities of distribution, common at rest, improved during exercise.

Andrus, Newman, Riley, Shulman and Bahnson [12] reported pulmonary function studies in two patients with mitral stenosis. They demonstrated that there was impairment of maximal breathing capacity, vital capacity

and diffusing capacity in both patients. There was also evidence of disturbance in distribution of both ventilation and circulation in each case, as shown by the elevated dead space and venous admixture ratios. These authors believed that impaired diffusing capacity was not the chief cause of the reduced exercise tolerance, but rather that the measurement of the diffusing capacity is a means of evaluating secondary changes in the pulmonary parenchyma and determining their reversibility.

Carroll, Cohn and Riley [11b] have recently reported in detail the distribution and diffusion characteristics of 29 patients with mitral stenosis. They found seven who had both normal diffusion and normal distribution, while the remainder had abnormalities of either diffusion or distribution, or both. They found that when alveolar dysfunction took the form of distribution abnormality there was usually reduction in vital capacity and maximal breathing capacity. They believe that such abnormalities arise mainly as a result of vascular congestion and at least minimal pulmonary edema. Defects in diffusion were related to structural changes in the diffusing surface, or possibly to vasomotor changes eliminating blood flow in some of the capillaries. In advanced cases they found defects in all aspects of pulmonary function that were studied.

Blount, McCord, Anderson and Komesu [13] measured alveolar and arterial oxygen tensions at two levels of oxygenation as described by Riley and associates.[14] They then calculated the oxygen diffusion capacity of the alveolar-capillary membrane and the venous admixture fraction. They found a significant decrease in the mean arterial oxygen tension and a normal alveolar oxygen tension. This resulted in an increase in the mean alveolar-arterial oxygen tension gradient. This indicated an impairment of oxygen diffusion across the alveolar-capillary membrane. Several patients were found to have an increased percentage of venous admixture in addition to impairment of diffusion. They believed that the impaired diffusion was the physiologic expression of the main pathologic changes in the alveolar-capillary membrane in mitral stenosis.

Discussion

Lewis and co-workers [1] have offered a very satisfactory explanation for the relationship of dyspnea and paroxysmal nocturnal dyspnea to mitral valve size and pulmonary arteriolar resistance. Those patients who have a narrow valve with only a slight increase in pulmonary arteriolar resistance frequently have their pulmonary bed acutely congested by a normally functioning right ventricle, with resulting dyspnea and paroxysmal nocturnal dyspnea. Those patients who have severe stenosis and moderate elevations of pulmonary arteriolar resistance have their pulmonary vascular bed protected from sudden surges of blood from the right ventricle. These individuals do not have disabling dyspnea. And, finally, those patients who have extreme elevations of their pulmonary arteriolar resistance have dis-

abling dyspnea. This may be related to the associated high pulmonary arterial pressures which accompany the elevated pulmonary arteriolar resistance, or it may be related to the low cardiac output associated with such high resistance.[1]

Ferrer and associates [3] have emphasized the fact that in patients who were dyspneic at rest or only on exertion, the pulmonary hypertension which was invariably present might be caused by the occurrence of left ventricular failure as well as by the mechanical block at the mitral valve and the changes occurring in the pulmonary vascular bed.

Andrus, Blalock and Bing [15] point out that pulmonary congestion decreases pulmonary elasticity, and the effusion of edema fluid in the pericapillary space (which may lead to fibrosis) interferes with diffusion. They believe both factors cause diminution in the respiratory function of the lungs.

Certainly there is an interplay of many factors causing the pulmonary dysfunction in mitral stenosis.

The stenotic valve orifice offers obstruction to the flow of blood from the pulmonary bed into the left ventricle. This results in pulmonary congestion and elevation of the pressure in the pulmonary circuit. This pulmonary hypertension or congestion may in some way—perhaps through decreasing the elasticity of the lung parenchyma—bring about dyspnea.

As the valve becomes more narrowed the pressure in the left atrium and pulmonary circuit has to rise in order to try to maintain an adequate cardiac output. If the pressure in the pulmonary capillaries is elevated much above the colloid osmotic pressure of plasma (25 to 30 mm. Hg) for any considerable length of time, transudation of fluid into the alveolar spaces may ensue, resulting in the clinical picture of pulmonary edema. Apparently as a protective device to forestall such an event, there develops probably both organic and functional narrowing of the small arterial radicles. This increase in pulmonary arteriolar resistance tends to increase an already elevated pulmonary artery pressure. Patients with moderately elevated pulmonary arteriolar resistance are troubled with moderate dyspnea but are no longer so likely to develop acute pulmonary edema. If the arteriolar resistance becomes enormously elevated dyspnea may become more severe, due presumably to the marked pulmonary hypertension and also to the lowered cardiac output from the failing right ventricle.

Because of the long standing pulmonary congestion and episodes of transudation there develops a thickening or fibrosis of the alveolar-capillary membrane. This tends to interfere with the normal diffusion of oxygen from alveoli to capillaries, and results in an increase in the alveolar-arterial oxygen tension gradient. This impairment of diffusion of oxygen across the alveolar-capillary membrane seems to be another factor in the production of dyspnea in patients with mitral stenosis.

The thickening of the capillary basement membrane and pericapillary fibrosis, with resulting decrease in permeability, seems to offer a plausible explanation for the failure of some patients with mitral stenosis to develop

pulmonary edema despite elevations of the pulmonary capillary pressure above the colloid osmotic pressure of plasma.[4, 7, 8]

In mild cases of mitral stenosis the vital capacity and maximal breathing capacity may be entirely normal. As the disease progresses the dyspnea that develops is usually out of proportion to the reductions found in these measurements of ventilatory function. Decreased lung resiliency secondary to pulmonary hypertension may interfere with maximal flow velocity.[9]

In severely incapacitated cases the occurrence of congestive failure and increased blood volume probably contribute to the reduction in total lung capacity.[9]

The occurrence of vascular congestion and pulmonary edema impairs distribution of blood and gas to the alveoli [11b] and brings about a reduction in the vital capacity and the maximal breathing capacity.

Summary

1. The various aspects of pulmonary function in patients with mitral stenosis are reviewed. There is a complex interplay of factors contributing to the pulmonary disability in patients with mitral stenosis.

2. Dyspnea which these patients experience is related to the size of the stenotic valve orifice, the level of the pulmonary arteriolar resistance, the degree of pulmonary hypertension, and to impairment of diffusion and distribution.

3. Pulmonary edema is likely to develop when the pressure in the pulmonary capillaries exceeds the colloid osmotic pressure of plasma. Failure to develop pulmonary edema at elevated pulmonary capillary pressures is due to a number of factors, such as the duration of the elevated pressure, the occurrence of thickening of the alveolar-capillary membrane, and the degree of the hydrostatic pressure gradient.

4. In general, patients with mitral stenosis who are asymptomatic show little alteration in their measurements of ventilatory function. As the disease progresses, however, there is diminution in vital capacity, maximal breathing capacity and breathing reserve.

5. In cases of mitral stenosis at rest there is a normal alveolar oxygen tension, a decreased arterial oxygen tension, and an abnormally large alveolar-arterial oxygen tension gradient. With exercise this gradient increases.

6. Several workers have demonstrated that in mitral stenosis there is impairment of the oxygen-diffusing capacity of the alveolar-capillary membrane. This is probably related to changes in permeability of the membrane secondary to long-standing pulmonary congestion and bouts of transudation.

7. Impairment of distribution of blood and gas to the alveoli is a result of the development of pulmonary vascular congestion and edema.

Acknowledgment

The author wishes to thank Dr. M. A. Blankenhorn and Dr. Johnson McGuire for their helpful criticisms and suggestions.

BIBLIOGRAPHY

1. Lewis, B. M., Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and physiological correlations in patients with mitral stenosis, V, Am. Heart J. **43**: 2, 1952.
2. Borden, C. W., Ebert, R. V., Wilson, R. H., and Wells, H. S.: Pulmonary hypertension in heart disease, New England J. Med. **242**: 529, 1950.
3. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Cournand, A., and Richards, D. W., Jr.: Hemodynamic studies in rheumatic heart disease, Circulation **6**: 688, 1952.
4. Ellis, L. B., Bloomfield, R. A., Graham, G. K., Greenberg, D. J., Hultgren, H. N., Kraus, H., Maresh, G., Mebane, J. G., Pfeiffer, P. H., Selverstone, L. A., and Taylor, J. A.: Studies in mitral stenosis: I. A correlation of physiologic and clinical findings, Arch. Int. Med. **88**: 515, 1951.
5. Draper, A., Heimbecker, R., Daley, R., Carroll, D., Mudd, G., Wells, R., Falholt, W., Andrus, E. C., and Bing, R. J.: Physiologic studies in mitral valvular disease, Circulation **3**: 531, 1951.
6. Gorlin, R., Haynes, F. W., Goodale, W. T., Sawyer, C. G., Dow, J. W., and Dexter, L.: Studies of the circulatory dynamics of mitral stenosis. II. Altered dynamics at rest, Am. Heart J. **41**: 30, 1951.
7. Araujo, J., and Lukas, D. S.: Interrelationships among pulmonary "capillary" pressure, blood flow and valve size in mitral stenosis. The limited regulatory effects of the pulmonary vascular resistance, J. Clin. Investigation **31**: 1082, 1952.
8. Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegl, R. J., and Dexter, L.: Factors regulating pulmonary "capillary" pressure in mitral stenosis, IV, Am. Heart J. **41**: 834, 1951.
9. (a) Frank, R. N., Cugell, D. W., and Gaensler, E. A.: Ventilatory function in mitral stenosis, J. Clin. Investigation **31**: 628, 1952.
   (b) Frank, R. N., Cugell, D. W., Gaensler, E. A., and Ellis, L. B.: Ventilatory studies in mitral stenosis, Am. J. Med. **15**: 60, 1953.
10. Blount, S. G., Jr., McCord, M. C., and Anderson, L. L.: The alveolar-arterial oxygen pressure gradient in mitral stenosis, J. Clin. Investigation **31**: 840, 1952.
11. (a) Carroll, D., and Riley, R.: Pulmonary vascular function in mitral stenosis, J. Clin. Investigation **31**: 620, 1952.
    (b) Carroll, D., Cohn, J. E., and Riley, R. L.: Pulmonary function in mitral valvular disease: distribution and diffusion characteristics in resting patients, J. Clin. Investigation **32**: 510, 1953.
12. Andrus, E. C., Newman, E. V., Riley, R. L., Shulman, L. E., and Bahnson, H. T.: The preoperative and postoperative management of some of the pulmonary complications of mitral stenosis, Tr. A. Am. Physicians **65**: 268, 1952.
13. Blount, S. C., Jr., McCord, M. C., Anderson, L. L., and Komesu, S.: The oxygen diffusion capacity of the alveolar-capillary membrane in mitral stenosis, Presented at the Midwestern Section of the American Federation for Clinical Research, Chicago, Nov. 6, 1952.
14. Riley, R. L., Cournand, A., and Donald, K. W.: Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: methods, J. Appl. Physiol. **4**: 102, 1951.
15. Andrus, E. C., Blalock, A., and Bing, R. J.: The surgical treatment of mitral stenosis and its physiological consequences, Tr. A. Am. Physicians **64**: 335, 1951.

PULMONARY ARTERIOVENOUS FISTULA AND TELANGIECTASIA *

By EUGENE WEISS, M.D., *South Bend, Indiana* and BENJAMIN M. GASUL, M.D., F.A.C.P., *Chicago, Illinois*

A FASCINATING chapter in the diagnosis and treatment of an uncommon pulmonary vascular lesion—pulmonary arteriovenous fistula—has been written since the turn of the century. In this disease, a saccular vascular dilatation occurs at the junction of a pulmonary artery and vein, causing shunting of blood without its passing through the lung capillaries, thus accounting for the symptom complex which occurs. Excellent reviews of the subject have been written by various authors.[1, 2, 3, 4] Churton [5] in 1896 is often credited with the first description of the pathologic entity, but Hedinger [6] in 1907 probably described the pathologic picture as we know it. Nauwerck [7] in 1923 described a case pathologically similar to Hedinger's. Klinck and Hunt [8] and Neiman [9] each described a case and gave a good clinical history, with the pulmonary findings in each case. (The last four cases are mentioned because they were not reviewed by the authors referred to above.)

To date there have been 149 case reports that we have reviewed, which include our own two cases, and three unpublished cases which we are reviewing from personal communications. Those new cases not previously reviewed are tabulated (table 1). An analysis of the 149 cases is presented in table 2.

In this group of 149 cases there are four in which the usual saccular dilatation or fistula was not found. Instead, numerous small telangiectasias were present through which the shunting of the unoxygenated blood occurred. The first case of this type was reported by Brink [10] in 1950, the second by Szutrely and Erdelyi [11] in 1951. Sloan and Cooley [4] wrote of an eight year old girl who had a surgical removal of her right middle lobe because of one large lesion, but whose remaining right lung was studded with innumerable tiny angiomas varying from 2 or 3 mm. to 1.5 or 2 cm. in size. Following the removal of her large lesion her cyanosis and clubbing persisted, and the authors felt that the shunting was occurring through the telangiectasias.

Our second case represents the fourth such reported case.

CASE REPORTS

Case 1. A 27 year old white male was perfectly well until eight years of age, when he first began to experience mild nosebleeds. At that time mild clubbing of the fingers and cyanosis were first noted. At 15 years of age an episode of epistaxis was

* Received for publication February 6, 1954.

TABLE 1

Reported Cases of Arteriovenous Fistula Not Included in Previous Reviews

Case	Author	Age	Sex	Familial Hemangiomas	Onset of Symptoms	Cyanosis	Clubbing	Dyspnea	Epistaxis	Hemangiomas	Hemoptysis	C.N.S. Symptoms	Bruit Over Lesion	Hemoglobin	Erythrocytes	Positive X-ray Findings	Angiography	Location	Treatment	Comment
1	Hedinger,[6] 1907	44	F								x	x						RLL		Died following surgery for a duodenal ulcer. Post mortem: a fistula-like structure of pulmonary vessels was found over the right lower lobe surface.
2	Nauwerck,[7] 1923	45	F						x		x	x						RLL		Died from hemorrhage due to erosion of a vascular cyst into a bronchus.
3	Klinck and Hunt,[8] 1933	46	F			x	x	x				x		90%				LUL		Sudden exitus from rupture of pulmonary varix located on the medial surface of the upper lobe.
4	Neiman,[9] 1934	57	M			x	x					x		80%	5.3	x		LUL		Exitus following cerebral vascular accident. A huge varix of the pulmonary vessels, left upper lobe.
5	Conklin,[10] 1948	30	M			x	x	x		x			0	137%	7.18	x	x	RLL	Segmental resection	Superior segment of the right lower lobe which contained the aneurysm was removed. Cyanosis and clubbing disappeared.
6	Garland and Anning,[11] 1950	6	M		1	x	x	0	x	x			x	136%	7.1	0		RML	Lobectomy	The presence of the bruit in the right axilla in a patient with a negative x-ray made surgery the logical next step. A lesion was found and removed in the right mid lobe, and the patient improved.
7	Garland and Anning,[11] 1950	6	F		7	x	x	x	x	x		x	x	108%	5.2	x		LUL	Local excision	X-ray diagnosis made of vascular lesion confirmed at surgery. Eight months later, looked well, but clubbing persists. Local excision.
8	Castellanos, Garcia, Diaz, and Anido,[12] 1950	5	F			x	x	x									x	RLL	Lobectomy	Right lower lobe resected, and because of the large dilatation of the pulmonary vein, part of the auricle was also resected.

TABLE 1—*Continued*

Case	Author	Age	Sex	Familial Hemangiomas	Onset of Symptoms	Cyanosis	Clubbing	Dyspnea	Epistaxis	Hemangiomas	Hemoptysis	C.N.S. Symptoms	Bruit Over Lesion	Hemoglobin	Erythrocytes	Positive X-ray Findings	Angiography	Location	Treatment	Comment
9	Rutishauser and Blanc,[16] 1950	2	M		5 mo.							x								Patient came to post mortem with enormous dilatation and hypertrophy, particularly of the right ventricle. Bronchiectasis, emphysema. There were numerous communications between arteries and veins, some of them with nodular enlargement connecting with venous sinusoids. Many of these were sites of fatty and hilar degeneration.
10	Blades and Beattie,[17] 1951	20	M	x	6	x	x	x	0	0			x	16.7	5.9	x	x	RLL		Recovery following surgery.
11	Marchand, Hejtmancik, and Herrmann,[18] 1951	24	M	x	Childhood	x	x	x	x	x		x	x	20 gm.	7.1	x		RLL RUL RML	Segmental resection	This patient had an associated subacute endarteritis.
12	Derra,[19] 1951	27	F		8–9	x	x		x	x	x	x	x	135%	7.5	x	x	RLL	Resection	
13	Szutrely and Erdelyi,[11] 1951	5	F	x	3	x	x	x	x	x			x	110%	5.2	x	x	All lobes		Angiography revealed increased densities in both lung fields, but no definite aneurysmal dilatation was noted. This was confirmed at post mortem, where no macroscopic shunts could be seen, but microscopically, examination revealed numerous P.A.V. dilatations.
14	Nixon and Perry,[20] 1952	26	M	x	8	x	x	x		x		x	x	137%	9.28	x		LLL	Total pneumonectomy. X-ray to cervical spine	Loss of cyanosis following surgery.
15	Conklin,[12] 1952	35	M			x	x			x			x			x	x	RLL	Segmental resection	A small arteriovenous fistula on the surface of the middle lobe was obliterated by suture ligature.

TABLE 1—*Continued*

Case	Author	Age	Sex	Familial Hemangiomas	Onset of Symptoms	Cyanosis	Clubbing	Dyspnea	Epistaxis	Hemangiomas	Hemoptysis	C.N.S. Symptoms	Bruit Over Lesion	Hemoglobin	Erythrocytes	Positive X-ray Findings	Angiography	Location	Treatment	Comment
16	Parker and Stallworth,[31] 1952	33	F			x	x		x			x	x	12 gm.	4.35	x		Left hilum	Dissection and excision of shunt	Recovery.
17	Andre, Dreyfus, and Brille,[32] 1952	46	F	0	23	x	x	x		0	0	x	x	115%	6.2	x	x	LLL	Lobectomy	Cyanosis disappeared, clubbing decreased, red count returned to normal.
18	Middelhoven,[33] 1952	5	F	0	4	x	x	0	0	0	0	0	x	132%	7.34	x		RUL		Following surgery, cyanosis disappeared and clubbing improved.
19	Lodin,[34] 1952	26	M		Childhood	x	x	0		0			x	122%	5.6	0	x	RML RLL		Death due to meningitis and brain abscess.
20	Wetzel and Heuck,[35] 1952	41	M	0	32		x			x	x	x	x	52%	3.7			RLL		
21	Freedman,[36] 1952	30	F	0		0	x						x	16.7 gm.	5.03	x		LLL		Surgery with recovery.
22	Freedman,[36] 1952	35	F	0			0	x		x		x	x	15.9 gm.	5.02	x	x	LLL		Surgery with recovery.
23	Talbot and Silverman,[37] 1952	48	M	0		0	0	0	x	0	0	x	0	14.5 gm.	4.8	0				
24	Meyersohn,[38] 1952	54	M			x	x				x		0		7.2	x		RML		Cerebral thrombosis after catheterisation. Died a few days later.
25	Schludermann,[39] 1952	44	F	x		0	0	0	x	x	0	x	x	32%	2.45	x		RLL		Surgery not done, because her case was asymptomatic.
26	Gray, Lurie, and Whittemore,[40] 1952	54	F	0		0	x		x	0			x	16.5 gm.		x		RLL	Lobectomy	Right lower lobectomy performed.
27	Gray, Lurie, and Whittemore,[40] 1952	32	M	0		0	0		x	0			x	15 gm.		x		LUL	Lobectomy	Left upper lobectomy performed.
28	Gray, Lurie, and Whittemore,[40] 1952	57	F	0		x	x				0		0	18.8 gm.		x		RLL RML	Lobectomy	Right middle lobe and right lower lobe lobectomy; also associated mitral stenosis, auricular fibrillation and congestive failure.

TABLE 1—*Continued*

Case	Author	Age	Sex	Familial Hemangiomas	Onset of Symptoms	Cyanosis	Clubbing	Dyspnea	Epistaxis	Hemangiomas	Hemoptysis	C.N.S. Symptoms	Bruit Over Lesion	Hemoglobin	Erythrocytes	Positive X-ray Findings	Angiography	Location	Treatment	Comment
29	Tobin and Wilder,[31] 1953	46	M		Childhood		x	x	x	x		x	x	10 gm.	4.22	x		LLL	Lobectomy	Subjective symptoms disappeared following surgery, also less epistaxis and pain.
30	Tobin and Wilder,[31] 1953	17	M	x		x	0		x	x		x	x	15.8 gm.	5.03			LML		Operation advised but not done because of reluctance of parents.
31	Stevenson,[32] 1953	58	M	x		x	x	0	x	x		x	x			x		RML	Antibiotics	Infected with septicemia. Two years later the lung lesions were unchanged but he was slightly anemic from frequent epistaxis. Not dyspneic, no cardiac enlargement. Murmur still present over lesion.
32	Israel and Gosfield,[33] 1953	41	F	x		0	0	0	x	x	x	x	0	13.6 gm.		x		LLL		Suggested hospitalization for surgical evaluation. Patient refused since she was asymptomatic. Admitted one year later, when death occurred due to hemoptysis.
33	Behnke, Lurie and Shumacker[34] 1953	26	M		18	x	x	x					0	17 to 20 gm.	5.7 to 7.1	x	x	RUL	Lobectomy	Improvement following surgery. Improvement of clubbing and maintained acyanotic state.
34	Massachusetts Gen. Hosp.,[35] 1953	32	F	0	17	x	x			x		x								Improvement following surgery.
35	Weiss and Gasul, 1953	25	M	0	13	x	x	x			x	x		144%	7.50	0				Death due to continued hemoptysis.
36	Weiss and Gasul, 1953	27	M	0	19	x	x	x	x	x	x	x		23.5 gm.	9.4	0		LLL		Died. Post mortem revealed a normal heart. A pulmonary arteriovenous fistula was found on the diaphragmatic surface of the left lower lobe. A sterile brain abscess was found.

TABLE 2

Findings in 149 Cases of Pulmonary Arteriovenous Fistula

Sex:	
Male	81
Female	65
Question	3
Familial History:	
Positive	40
Negative	40
Question	69
Age at Diagnosis:	
Youngest	2 days
Oldest	79 years
Number of Lesions:	
One	95
Bilateral	15
Multiple	37
Location:	
Inferior Lobe	90
Middle	33
Superior	28
Question	20
Lung Field:	
Right	100
Left	64
Question	9
Age Symptoms Appeared:	
At Birth	13
Before 12 years	42
After 12 years	44
Question	50
Cyanosis:	
Positive	114
Negative	22
Question	13
Clubbing:	
Positive	113
Negative	28
Question	8
Dyspnea:	
Positive	82
Negative	21
Question	46
Epistaxis:	
Positive	50
Negative	15
Question	84
Polycythemia:	
Positive	99
Negative	13
Question	37
Hemangiomas:	
Positive	59
Negative	16
Question	74
Hemoptysis:	
Positive	41
Negative	19
Question	89
C.N.S. Symptoms:	
Positive	100
Negative	16
Question	33
Bruit:	
Positive	79
Negative	33
Question	37

so severe that cauterization was required. At this time the diagnosis of congenital heart disease was first made by the family physician and by an internist to whom he was referred. His complaints had also included some dyspnea on exertion, as well as frequent attacks of dizziness. As he grew older the symptoms continued and were aggravated by paresthesias, particularly of the upper extremities.

In April, 1947, when he was 23 years old, he was examined at the Cardiac Clinic at the Johns Hopkins Hospital. Their findings included "cyanosis, normal blood pressure, pulse 92 with regular sinus rhythm. Heart sounds were of fair quality and somewhat distant. There was a faint apical systolic thrill palpable and rather a remarkable sparsity of murmurs. A very short systolic murmur was heard at the lower left sternal border and towards the apex, but appeared to be hardly more than a split first sound. The lungs were clear. He had clubbing and cyanosis of the fingers.

"Fluoroscopically, the heart was elongated with a slight fullness of the pulmonary conus. There were increased vascular markings bilaterally, with minimal pulsations, except in the large branches of the pulmonary artery at the hilus. In the right anterior oblique there was slight fullness in the pulmonary conus and in the left anterior oblique the pulmonary window was only slightly hazy, but there was evidence of a large pulmonary artery. Barium swallow revealed a left aortic arch, with no evidence of any retroesophageal vessels. Circulation time measured 14½ seconds.

"Arterial oxygen studies were as follows: content 23.03 vol. %; capacity 28.55 vol. %; giving a saturation of 80.75%; CO_2 was 30.4 vol. %; red count 9.4 million; hemoglobin 23.5 grams and hematocrit 75.2.

"EKG showed right axis deviation and in the unipolar precordial leads evidence of right ventricular hypertrophy.

"Because of the relative sparsity of pulsations in the presence of such marked increase in vascular markings, pulmonary stenosis with an auricular septal defect was considered. However, it was thought with the unusually late appearance of cyanosis it seemed more likely that the patient would come in the Eisenmenger group. Because of the confusion between the two diagnoses, Dr. Bing's studies were considered in order. An exercise test was done and showed that the oxygen consumption per litres of ventilation rose as it does in most of the Eisenmenger group and consequently considered that this was the likely diagnosis." Since that time Bing has shown that the same results would be expected in pulmonary arteriovenous fistula as those obtained in the Eisenmenger group.

In May 1947, the patient began to experience episodes of abdominal distress. Barium studies revealed a constant ulcer deformity of the duodenum, for which he was given symptomatic therapy.

In 1949 he was examined by us. The essential findings were marked clubbing of the fingers and toes, with cyanosis of the lips, hands and feet. Numerous telangiectasias of the face and trunk were seen. The heart was not enlarged to percussion. There was an inconstant grade 1 or 2 systolic murmur over the third and fourth interspaces.

Fluoroscopic examination in routine positions showed no cardiac chamber enlargement. There were two normal sized pulmonary arteries which pulsated more than normal, but the pulmonary vascular markings in the peripheral lung fields appeared to be somewhat diminished. There were no evidences of any large pulmonary arteriovenous aneurysms. The blood count revealed: red blood cells 8.4 million; white cells 9,100; hemoglobin, 124.4 per cent; color index, 0.73; reticulocytes, 2.5%; platelets, 308,000; coagulation time, 9 minutes (Lee and White); bleeding time, 7 minutes; hematocrit, 67.

Catheterization findings (performed by Dr. O. Prec) were as follows:

Position	*Oxygen Vol. %*	*Systolic Pressure mm. Hg*	*Diastolic Pressure*
R. P. A.	12.16	14	2
R. V.	11.67	14	−2 to 2
R. V.	11.06		
R. A. low.	10.87		−2 to 2
R. A. mid.	10.29		
R. A. high	9.27		
O_2 consumption	360 c.c./min.		
Art. O_2 saturation	74%		
Systemic flow	16.7 L./min.		
A-V O_2 difference	2.16 Vol. % (Patient very excited by catheterization)		
Additional observations:			
Vital capacity	4570 c.c.		
Ventilatory capacity	146 c.c.		
Resting ventilation	14.95		
Ventilation equiv. for O_2	4.1		

The patient remained relatively well receiving symptomatic therapy, until August 23, 1951, when, following a convulsive seizure, he developed a left hemiplegia. He

improved temporarily but then became more severely ill, with more widespread involvement, and died on September 8, 1951.

Angiocardiography was not done in this case for several reasons. First, the absence of any lesions visible on routine postero-anterior and oblique films, and on fluoroscopy in a patient who reacted poorly to catheterization made us reluctant to go ahead with angiocardiography, which at that time had not yet been thoroughly emphasized as a diagnostic procedure in this disease.

Post mortem (performed by Dr. H. J. Williams) revealed the following:

Heart: No excessive fluid was present in the pericardial cavity, and the heart moved freely in the pericardial sac. Grossly, the heart did not appear enlarged. It weighed 295 gm. The subepicardial fat was normal in distribution and amount. The myocardium of the left ventricle measured 3 mm. in thickness, which is the upper limit of normal. Slight dilatation of the right ventricle was present. Several small fibrotic areas measuring up to 2 mm. in diameter were present in the myocardium of the interventricular septum. No valvular deformities were present. The coronary vessels were relatively free of atherosclerosis. No abnormalities of the great vessels were demonstrable.

Lungs: The right lung weighed 305 gm., and the left lung 290 gm. Both lungs felt crepitant throughout. Present near the anterior margin of the diaphragmatic surface of the lower lobe of the left lung was a bleb measuring approximately 4 cm. in diameter, filled with dark material resembling blood. Dissection of the pulmonary vascular tree to the left lower lobe revealed the arteries and veins near the periphery of this structure to be considerably enlarged in caliber, and several large arteries and veins could be seen communicating with this subpleural bleb. The bleb appeared to be lined by endothelium. The bleb could be filled by injection of fluid into one of the communicating arteries or veins, and represented an arterial venous aneurysm. Dissection of the left upper lobe and the right lung failed to reveal any further arteriovenous aneurysms.

Brain: The brain weighed 1,375 gm. The meninges were normal in appearance. Coronal sections through the brain revealed the presence of a large abscess in the central portion of the right cerebral hemisphere. The abscess measured approximately 4.5 cm. in diameter and was filled with foul-smelling liquid pus. The abscess was bounded medially by the right lateral ventricle and supralaterally by the surface of the right cerebral hemisphere. The abscess had a wall which measured approximately 0.5 mm. in thickness and was firm, suggesting the abscess to be of some duration. The brain parenchyma over the most superficial portion of the abscess was thinned and measured only 1 mm. in thickness. The gray matter of the brain for a distance of approximately 2 cm. anterior to the abscess and 1.5 cm. posterior to the abscess contained numerous petechiae. The abscess contents were sterile on culture. No extension of the abscess cavity into the right lateral ventricle was present.

No unusual features were present in the stomach or esophagus. A slight degree of wrinkling was present in the first part of the duodenum, but it was difficult to tell grossly whether that represented the site of a former duodenal ulcer or not. No lesions were present in the remaining portion of the small bowel or in the large bowel.

Summary: This 27 year old white male with a history of cyanosis, clubbing, dyspnea, epistaxis, cutaneous hemangiomas, hemoptysis, CNS symptoms and polycythemia had no AV lesions demonstrable by x-ray or fluoroscopy. They were looked for but were not found. Post mortem revealed an aneurysm behind the heart.

Case 2. A 25 year old white male first noted dyspnea on exertion and cyanosis of the lips and fingers at the age of 13. Sometimes a cough productive of yellowish sputum accompanied these symptoms, and on some occasions the sputum was blood-

tinged. At no time was he aware of any chill or fever. He said he tired easily but was able to climb three flights of stairs or walk several blocks before finding it necessary to rest. He slept on one or two pillows at night. He never experienced chest pain nor ankle swelling. He understood that he had been a normal baby, and that early development had not been remarkable. He had done poorly in his school work and failed several grades, and was not graduated from grammar school until he was 16 years old. Family history was noncontributory.

He was first admitted to another hospital on March 6, 1949, with a one week history of anorexia, slight nausea and postprandial abdominal distention. Pain and vomiting were absent. The discomfort was relieved by alkali, but food and milk accentuated it.

Physical examination at that hospital revealed a poorly nourished and underdeveloped young male who was dyspneic and orthopneic. Blood pressure was 120/90 mm. of Hg; temperature, 100° F. The buccal mucosa was hyperemic, and there was clubbing of the fingers. The heart was not enlarged. The aortic second tone was louder than the pulmonic, and the first tone at the apex was split. Wheezing râles were heard in all lung fields.

Laboratory examination revealed the following: hemoglobin, 18 gm.; red cells, 6.45 million; white cells, 3,950, with a normal differential. The venous pressure was 12.6 cm. water. The circulation time was 16 seconds with Decholin and 13 seconds with ether. X-ray of the chest revealed increased bronchovascular markings, but the heart size was normal. Cardiac catheterization studies, performed by Dr. J. Campbell, of the Presbyterian Hospital, revealed the oxygen content to be: right pulmonary artery, 21.1 vol. per cent; right ventricle, 20.5 vol. per cent; right auricle, 20.5 vol. per cent; superior vena cava, 20.9 vol. per cent; inferior vena cava, 19.0 vol. per cent. The pressure in the pulmonary artery and the right ventricle was reported as normal. Oxygen inhalation studies revealed: initial arterial oxygen saturation, 77.6 per cent; after 30 seconds of 100 per cent oxygen, 85.8 per cent; after one and one-half minutes, 89.5 per cent; after three minutes, 93.7 per cent; and after eight minutes, 94.3 per cent.

After the completion of these diagnostic procedures the patient was discharged. He was admitted to Cook County Hospital on November 25, 1949, with essentially the same symptoms as before.

Physical examination revealed a poorly nourished white male in no distress. His temperature was 98° F.; pulse, 88; respirations, 20. The blood pressure was 118/80 mm. of Hg in the left arm and 120/82 mm. of Hg in the right arm. He was markedly cyanotic and mentally dull. The chest was clear and the heart normal. A_2 was louder than P_2. The liver and spleen were not palpated, but there was moderate tenderness in the right upper quadrant. There was clubbing of the fingers. The urine showed a 4 plus urobilinogen but was otherwise negative. The hemoglobin was 142 per cent; red blood cells, 7.21 million; white blood cells, 5,300, with a normal differential. The serum chlorides were 113 mEq/L.; sodium, 140.8 mEq/L.; carbon dioxide combining power, 40 vol. per cent. X-ray of the chest revealed the heart size to be normal; there were increased bronchovascular markings, and both diaphragms were reported low. On November 28, 1949, while in the hospital, the patient had a massive hematemesis and melena. The pulse rose to 140 and the blood pressure dropped to 80/50 mm. of Hg. The bleeding continued and the patient remained seriously ill for one week in spite of oxygen, blood transfusions and fluids. He was disoriented, and had bilateral Babinski's and Hoffmann's reflexes. There was no nuchal rigidity. The bleeding stopped, the neurologic signs disappeared and the patient improved. Barium studies revealed a large duodenal ulcer. The patient was discharged and advised to follow a bland diet and alkali medication.

He was re-admitted on March 1, 1951. On admission the hemoglobin was 130 per cent; red blood cells, 7.51 million; white cells, 3,700, with a normal differential.

The urine was negative. X-ray of the chest was reported as showing a normal sized heart with straight left border. There were diffuse, strandlike infiltrations with small nodulations in both lung fields.

Because an arteriovenous aneurysm was suspected an angiogram was done. This revealed no gross evidence of a visible mass, as would be expected in a typical arteriovenous aneurysm. All that was seen were increased vascular markings extending peripherally in both lower lobes, particularly the left.

His final admission was on August 5, 1951. He had neglected his diet and medication. His epigastric distress had returned and he had vomited blood repeatedly for one day. The pulse was 124, and the blood pressure 118/80 mm. of Hg. The physical examination was unchanged except that a soft systolic murmur was heard over the entire precordium, and the liver was palpated 2 cm. below the costal margin. The hemoglobin was 144 per cent; red cell count, 7.50 million; white cell count, 6,400, with a normal differential. Bleeding continued and the patient gradually went downward in spite of blood transfusions, fluids, oxygen, Levine suction and tracheal aspiration. He died on August 8, 1951, more than two years after the first hospital admission.

Post mortem (performed by Dr. P. B. Szanto) revealed the following:

Heart: The heart weighed 350 gm. and was heavier than normal. The apex of the heart was formed by the left ventricle. The epicardium was smooth and glistening. The wall of the left ventricle was 20 mm. and that of the right ventricle was 4 mm. in thickness. The aortic valvular ring measured 7 cm., the pulmonary 8 cm., the mitral 11 cm., and the tricuspid 11.5 cm. There was moderate thickening at the line of closure of the mitral. The myocardium was brownish red.

Lungs: The lung on the left side weighed 1,025 gm. and that on the right 525 gm. They were very firm and almost airless. The cut section was dark red; upon opening, the corresponding bronchi contained much blood. The right lung was moderately well aerated. The cut surface was moist and edematous, and considerable bloody, frothy fluid oozed from the surface. Microscopically, sections revealed hemorrhage in the alveoli. Slight thickening of the alveolar septa was seen. Heart failure cells were scattered throughout the section. Section taken from the left lower lobe revealed dilatation of the precapillary vessels in the lung. This picture somewhat resembled telangiectasis.

Liver: The liver weighed 825 gm. and was smaller than normal. The edges were sharp and the color was a tan-purple. On cut surface, nodular areas of various sizes were seen. One nodular area was yellow and had a scalloped margin; it was firm and the center was softer, showing some hemorrhage. The lobular markings were normal. The gall-bladder contained about 20 c.c. of bile and was otherwise normal. Microscopically, the lobular pattern of the liver was well preserved. The liver cells contained large amounts of lipofuscin, especially around the central veins. In the portal field there was a marked proliferation of the bile ducts. The nodules seen grossly showed bile duct and liver cell proliferation. The liver cells within the nodules contained small and large vacuoles. These nodules were quite vascular and areas in them resembled telangiectasis. Within the nodules, the liver cell plates were several cells thick.

Kidneys: The kidneys weighed 550 gm. and were larger and heavier than normal. The capsule stripped with some difficulty, leaving a finely granular surface. The arcuate arteries were dilated. On cut surface the corticomedullary border was sharp. The medulla was darker than the cortex. On the surface were a few nondepressed, spider-shaped areas. The remainder of the kidney was normal.

Summary: This 25 year old white male with a history of dyspnea, cyanosis and episodes of hemoptysis of eight years' duration developed a polycythemia. The gross and microscopic examination of the lung revealed a

pulmonary fibrosis of moderate degree. There was evidence of hemorrhage into the lung. The microscopic examination of the left lower lobe revealed foci of distended, congested precapillary vessels. This was interpreted as a pulmonary telangiectasia. The possibility exists that this telangiectasia entered as an arteriovenous communication, in which case the picture of polycythemia and clubbed fingers would be a secondary typical complication to the pulmonary finding. The pulmonary fibrosis per se was not sufficient to explain the polycythemia. The duodenal ulcer could be interpreted as a typical complication secondary to polycythemia. The cause of death was a massive hematemesis with aspiration of the blood into the lungs.

Discussion

The syndrome of cyanosis, clubbing of the fingers and polycythemia, in the presence of a normal heart, with x-ray evidence of what appears to be a localized pulmonary lesion of vascular origin, makes the diagnosis of a pulmonary A. V. shunt almost a certainty.

Embryologically, there appears to be in this disease a defect in vascular formation, since unoxygenated blood is shunted directly from a branch of the pulmonary artery which carries unoxygenated blood to one or more pulmonary veins without passing through capillaries. A saccular distention is usually present at their junction. That a general vascular dysplasia, similar to Weber-Osler-Rendu syndrome, is present is manifested by the frequency of telangiectasia, often hereditary, in numerous parts of the body. These shunts may be single or multiple, and may occur early or late in life. After one such lesion has been removed surgically, and evidence indicates that no other lesion is present, a new lesion may subsequently become manifest. They may occur in any portion of the lung and may be bilateral, but are more often unilateral, and are found most often in the lower lobe, usually on the right side. The condition has been found with equal frequency in both sexes.

The afferent and efferent vessels may become enlarged, the latter becoming tortuous and appearing as varicosities. Their walls may be thinned and be the site of atheromatous degeneration and may contain thrombi, at times of considerable size. They may be the site of bacterial endarteritis.

From the description of the pathologic lesion the clinical picture becomes more readily understandable. Cyanosis is the most common feature of the disease, and is the result of the shunting of unoxygenated blood to the general circulation; but it is also aggravated by the plethora of the compensatory polycythemia created by the shunt. The cyanosis is not associated with any subjective evidence of illness, and is usually out of proportion to the amount of dyspnea, when it finally develops.

Clubbing of the fingers is the next most frequent sign, being present in this disease as in congenital cardiacs with cyanosis.

The compensatory polycythemia usually reaches 6,000,000 to 7,000,000 red blood cells; but counts exceeding 10,000,000 with hematocrits up to 90

have been described. However, the blood picture may be normal, or anemia may be present at times as a consequence of severe and repeated bleeding from hemoptysis or from the gastrointestinal tract. There is an associated elevation in blood volume, but, unlike peripheral arteriovenous aneurysms, the increase in volume results from the increase in red cell volume, the plasma volume remaining unchanged. Blood pressure and cardiac size are also unaffected by these shunts. The polycythemia is differentiated from that of primary polycythemia in that there is no increase in the white cells or platelets, and the spleen is usually normal.

Dyspnea on effort is a common finding but is usually not so severe as one would expect from the degree of cyanosis. Many of the patients were capable of work at arduous trades.

The hemangiomata are manifestations of the underlying generalized, usually hereditary, vascular dysplasia. They may be present on the skin or mucous membranes, and, when present in the nose or mucous membrane lining of the respiratory or gastrointestinal tracts, their weak walls make them more liable to rupture, accounting for the frequent episodes of epistaxis or hemoptysis or hematemesis. The shunt itself may rupture into a bronchus and lead to sudden fatal hemorrhage.

Central nervous system manifestations of the disease are numerous and varied. There may be headaches, vertigo, weakness, fainting attacks, dizziness, paresthesias, pains, diplopia, repeated epileptiform seizures, and even hemiplegias. Such symptoms have been ascribed to cerebral anoxia due to the decreased arterial blood oxygen saturation, to the plethora, to angiomata in the brain with or without associated thrombosis, to air emboli arising from the pulmonary arteriovenous shunts, and, lastly, to abscesses which are occasionally seen post mortem in these individuals.

Chest pains have been variable, some being attributed to the lesion itself, and some to the associated coronary insufficiency which theoretically may be present on the basis of the anoxia.

Roentgenologically, a lobulated or round discrete mass is usually seen with two or more linear shadows connecting the mass with the hilum. These linear shadows represent the afferent and efferent vessels; they are usually larger than other vessels in their vicinity, and their course is more tortuous. Fluoroscopically, the mass may be seen to decrease in size in Valsalva's maneuver and to increase in size in Müller's maneuver.

Routine films may fail to show the presence of a lesion. It is for that reason that angiography in the postero-anterior and oblique views and tomography should be done routinely in all suspected cases, particularly when surgery is contemplated. A lesion obscured by the diaphragm or heart may be brought out only by this method. This was particularly emphasized by our first case, in which the lesion was suspected and looked for but was not seen by routine fluoroscopy and postero-anterior and oblique x-ray films.

As mentioned previously, this malformation is manifested by shunting

of the unoxygenated pulmonary artery blood to the pulmonary vein via an enlarged fistulous or saccular junction. Our first case is an example of this more common type.

Our second case is an example of the second type, in which the findings in the heart and chest x-rays are normal. On angiocardiography no definite rounded lesion is seen, as in the usual cases. Instead, only an area of increased vascular markings may be noted if the dysplasia is present in one or more particular areas. These lesions probably are the precursors of the larger lesions.

In his discussion on the pathogenesis of these lesions, Giampalmo comments on the double vascular supply of the lung, namely, pulmonary and bronchial systems, referring to various embryologic studies in which the anlage of these systems would make them more prone to angiomatous dysplasias. It is interesting that in our second case these dysplasias were found in the lung and liver, both organs which have a double blood supply.

These patients are frequently misdiagnosed as congenital heart disease, because of the clubbing and cyanosis. Tuberculosis and lung tumors are suggested by the hemoptysis and roentgenologic lung lesions. Ayerza's disease, methemoglobinemias and sulfhemoglobinemias may be considered because of the cyanosis. A primary rather than a secondary polycythemia may be thought of.

Summary

1. The cases of pulmonary arteriovenous fistulas have been collected from the world literature; two new cases of our own are added, and three from personal communications. (Table 1, cases 35, 36 and 5, 15, 33.)

2. Emphasis is placed on the need for angiocardiography in addition to routine films and fluoroscopy for conclusive diagnosis, and, when surgery is anticipated, in order to see all the lesions.

3. Our second patient is the fourth example reported in the world literature, in which only telangiectasia can account for the symptoms, no saccular dilatation having been found.

BIBLIOGRAPHY

1. Yater, W. M., Finnegan, J., and Griffin, H. M.: Pulmonary arteriovenous fistula, J. A. M. A. **141**: 581, 1949.
2. Giampalmo, A.: The arteriovenous angiomatosis of the lung with hypoxemia, Acta med. Scandinav. Suppl. **284**: 1, 1950.
3. Moia, B., and Albanese, A. R.: Arteriovenous pulmonary fistula, Rev. argent. de cardiol. **17**: 7, 1950.
4. Sloan, R. D., and Cooley, R.: Congenital pulmonary arteriovenous aneurysm, Am. J. Roentgenol. **70**: 183, 1953.
5. Churton, T.: Multiple aneurysm of pulmonary artery, Brit. M. J. **1**: 1223, 1897.
6. Hedinger, Herr: Demonstration eines Lungenvarix, Verhandl. d. deutsch. path. Gesellsch. **11**: 303, 1907.
7. Nauwerck, C.: Varix of lung and hemoptysis, München. med. Wchnschr. **33**: 1004, 1923.

8. Klinck, G. H., Jr., and Hunt, H. D.: Pulmonary varix with spontaneous rupture and death, Arch. Path. **15**: 227, 1933.
9. Neiman, B. H.: Varix of the pulmonary vein, Arch. Path. **17**: 135, 1934.
10. Brink, A. J.: Telangiectasis of lung, with two case reports of hereditary hemorrhagic telangiectasia with cyanosis, Quart. J. Med. **19**: 239, 1950.
11. Szutrely, G., and Erdelyi, M.: Arteriovenous fistula of the pulmonary vessels, Magy. Radiol. **3**: 145, 1951.
12. Bing, L. J., Vandam, L. D., and Gray, F. S., Jr.: Physiological studies in congenital heart disease. III. Results in five cases of Eisenmenger's complex, Bull. Johns Hopkins Hosp. **80**: 323, 1941.
13. Conklin, W. S.: Personal communications, 1948, 1952.
14. Garland, H. G., and Anning, S. T.: Hereditary hemorrhagic telangiectasia, Brit. M. J. **1**: 700, 1950.
15. Castellanos, H., Garcia, O., Diaz, A., and Anido, H.: Arteriovenous aneurysm of the pulmonary circulation, J. internat. chir. **10**: 223, 1950.
16. Rutishauser, E., and Blanc, W.: Anastomoses arterio-veineuses glomiques du poumon avec syndrome d'insuffisance droit et cyanose, Schweiz. Ztschr. f. Path. u. Bakt. **13**: 61, 1950.
17. Blades, B., and Beattie, E., Jr.: Pulmonary arteriovenous aneurysm, J. Mt. Sinai Hosp. **18**: 195, 1951.
18. Marchand, E. J., Hejtmancik, M. R., and Herrmann, G. R.: Extracardiac arteriovenous fistulas in the thorax, Am. Heart J. **42**: 682, 1951.
19. Derra, E.: Congenital arteriovenous pulmonary fistula and its surgical therapy, Zentralbl. f. Chir. **76**: 1362, 1951.
20. Nixon, J. W., and Perry, J. F.: Arteriovenous fistula of the lung and an associated hemangioma of the vertebra, Dis. of Chest **21**: 108, 1952.
21. Parker, E., and Stallworth, J. M.: Arteriovenous fistula of the lung treated by dissection and excision without pulmonary excision, Surgery **32**: 31, 1952.
22. Andre, R., Dreyfus, B., and Brille, D.: Arteriovenous aneurysm of the lung; lobectomy; cure, Bull. et mém. Soc. méd. d. hôp. de Paris **68**: 646, 1952.
23. Middelhoven, A.: Arteriovenous fistula in the area of the pulmonary artery, Maandschr. v. kindergeneesk. **20**: 157, 1952.
24. Lodin, H.: Tomographic analysis of arteriovenous aneurysms in the lung, report of a case confirmed at autopsy, Acta radiol. **38**: 205, 1952.
25. Wetzel, U., and Heuck, F.: Arteriovenous aneurysms of the lungs and similar abnormalities, Fortsch. Röntgenstrahl. **77**: 335, 1952.
26. Freedman, M. J.: Asymptomatic pulmonary arteriovenous fistula: report of two cases surgically treated, Am. Heart J. **44**: 594, 1952.
27. Talbot, T. J., and Silverman, J. J.: Asymptomatic arteriovenous fistula of the lung, Arch. Int. Med. **90**: 569, 1952.
28. Meyersohn, S.: Pulmonary arteriovenous fistula, Brit. J. Radiol. **25**: 614, 1952.
29. Schludermann, H.: On congenital and acquired aneurysms of the pulmonary artery, Fortsch. Röntgenstrahl. **76**: 8, 1952.
30. Gray, F., Jr., Lurie, P. R., and Whittemore, R.: Circulatory changes in pulmonary arteriovenous fistula, Yale J. Biol. and Med. **25**: 107, 1952.
31. Tobin, J. R., Jr., and Wilder, T. C.: Pulmonary arteriovenous fistula associated with hereditary hemorrhagic telangiectasis: a report of their occurrence in a father and son, Ann. Int. Med. **38**: 868, 1953.
32. Stevenson, F. H.: Infected arteriovenous fistula in the lung, Lancet **1**: 626, 1953.
33. Israel, H., and Gosfield, E., Jr.: Fatal hemoptysis from pulmonary arteriovenous fistula, J. A. M. A. **153**: 40, 1953.
34. Behnke, R. H., Lurie, P. R., and Shumacker, H. B., Jr.: Personal communication, 1953.
35. Case Records of the Massachusetts General Hospital; Case 39302, New England J. Med. **249**: 156, 1953.

SCLERODERMA (BASED ON A STUDY OF OVER 150 CASES) *

By Irving Leinwand, M.D., A. Wilbur Duryee, M.D., F.A.C.P., and Maurice N. Richter, M.D., *New York, N. Y.*

Scleroderma is not a common disease, nor is it rare. The first description of this condition is credited to Curzio [1] of Naples in 1752. Since that time there have been hundreds of cases described. It has often been reported in association with dermatomyositis, which it closely resembles.[2-8] Scleroderma was first regarded as primarily a skin disease. Any systemic complaints for the most part received scant attention, since the skin lesions far overshadowed other symptoms. In reviewing the history of scleroderma one is impressed by the metamorphosis of opinion regarding the classification of this disease.[9, 10] This is due mainly to the obscurity of its etiology, and the myriad theories attendant upon such a situation.

Although the literature of the past few years has presented increasing evidence that scleroderma is a disease in which pathologic changes are generalized, this concept is not a new one. In 1898 Steven [24] presented an excellent description of a case of scleroderma, with postmortem findings which demonstrated the generalized nature of the pathologic processes. He noted changes in the vessels of the pons, medulla and cord. (The entire brain was not studied histologically.) He noted that the arteries were often surrounded by homogeneous, structureless material. The coats of some of the arteries were thickened. He stated that both kidneys showed unmistakable signs of interstitial nephritis. There was also evidence of recent parenchymatous inflammation. His description of the skin was similar to that in all recent reports. In 1898 Osler [34] likewise emphasized the fact that scleroderma was a generalized disease. He stated: "We know really nothing of the essential causes, and the data is not yet at hand upon which a satisfactory theory can be based. The disease is variously regarded as a trophoneurosis dependent upon changes in the nervous system; a perversion of nutrition analogous to myxedema and due to disturbance of the thyroid function; a sclerosis following wide-spread endarteritis; a primary slow hyperplasia of the collagenous intercellular substance of the corium or a primary affection of lymph channels, central or peripheral."

For the next 25 years there was a tendency to focus attention solely on the skin lesions. In the last decade, however, many articles have appeared confirming the systemic nature of the disease. Despite these recent reports relatively little pathologic material has been reported.

* Received for publication November 23, 1953.

From the Departments of Medicine and Pathology, New York University Post-Graduate Medical School and the University Hospital, New York, N. Y.

Material

To establish the clinical and pathologic picture of this disease, a long term study involving a substantial number of patients was undertaken. In presenting this study we will describe the disease as it affects each system. This study covered a period of approximately 14 years and included over 150 cases. The group of patients studied was from the Peripheral Vascular Clinic of the New York University Post-Graduate Medical School, the University Hospital, and from the private practices of its members. It was impossible to do all studies on all patients. Of the 150 cases studied, 25 were of the circumscribed type. The diagnosis was confirmed by biopsy in the majority of the cases.

Sex Incidence: In this series of 150 patients there were 108 females and 42 males, a ratio of females to males of about 2.7 : 1. This same ratio was approximately true of the 22 patients known to have died; females 16, males 6, about 2.7 : 1. Due to the displacement of the population during and after the war, less than 50 per cent of the pre-war patients could be found to determine their disposition.

Age: There was great variation in age at onset: the youngest was three years, the oldest 65. Seventy per cent of our cases developed between the ages of 20 and 50.

Race: This is largely a disease of white-skinned people. There were three Negroes among 150 patients. There was no apparent racial selection in this group.

Heredity: Neither in our own series nor in the literature have we been able to trace a single instance of the disease occurring in any other member of a family or, as far as we could learn, in any other generation. All children of our patients with scleroderma were normal.

Duration: The duration varies widely. One patient died eight months after the earliest clinical signs of the disease. One patient is still living who has had scleroderma for 30 years.

Symptoms

The earliest symptoms are usually swelling and stiffness of the skin of the hands and of the face. Pain in the joints is almost always present and may precede any apparent skin changes, so that arthritis is a not uncommon diagnosis in the early phase of this disease. Soon there is limitation of motion in the fingers. Contracture deformities may take place. The patient may notice decreased mobility of the skin of the face, and the wrinkles of the face may disappear. The patient may have difficulty in opening his mouth as completely as in the past. The patient with dentures may have difficulty in removing and inserting them. Sensitivity to cold may be pronounced. Loss of weight, weakness and fatigue soon follow in the generalized cases. Bronze pigmentation of the skin may be present. Ulcerations of the skin are common and occur usually at the fingertips or over the joints.

However, ulcerations also occur in areas without relation to any joint, and are even found in some cases of circumscribed scleroderma. Headache is a common complaint and is not confined to any particular area. Difficulty in swallowing is an important symptom of esophageal involvement. There may be other gastrointestinal complaints, such as vague abdominal pain, epigastric distress, constipation or diarrhea. Cough is not uncommon. Palpitation and dyspnea on exertion are late complaints and indicate pulmonary or cardiac involvement. In contrast to many other chronically ill patients, most of these have mental depression.

Physical Findings

In the early stages the skin appears to be shiny and swollen, so that the skin on the fingers is drawn tight and the fingers are actually slightly thicker than normal. The skin cannot be picked up in folds or wrinkled, and it may be firm and waxlike. After the acute stage has subsided, sclerosis of the subcutaneous tissues takes place and the skin becomes even more rigid. Pigmentation of the skin may be pronounced (figure 1). The mouth cannot be fully opened. The skin of the face becomes taut so that the lines of expression are smoothed out. The lips become thin and shortened, the nose is sharp and pinched. Rarely, the ears are involved. There may be marked limitation of motion of the extremities due to contraction deformities. A

Fig. 1. Generalized scleroderma, showing marked pigmentation of the skin with tightening of the skin of the face (fatal case).

generalized case may present a varied picture, showing the earliest stage of a shiny atrophied skin in the most proximal part, a thick waxy edematous skin at a transitional area, and a sclerotic pigmented region at the oldest distal portion.

Ulcers may be seen as small, punched-out areas, usually at the extreme tip of the finger, or close to the nail. Paronychiae are a common complication. Ulcerations over the joints usually contain small deposits of calcium which form the center of the ulcer, or the ulcer may consist merely of a rounded shallow crater with a slightly erythematous background. Where the ulcer has healed, a depressed scar may be present. The most common sites for these ulcers are over the phalangeal joints, the elbows, the knees

FIG. 2. Hands of the patient seen in figure 1. Note joint changes with ulceration and calcinosis over the middle phalangeal joint, third finger, left hand.

and the ankles. With sclerodactylia the fingers are shortened and rounded, and the nails are decreased in size and curve over the finger tips. In these cases, x-ray visualization reveals the disappearance of the terminal tufts (figure 3). Occasionally, the entire distal phalanx is absent.

Raynaud's syndrome may precede, occur concurrently with, or follow the onset of this disease. Practically all of these patients are sensitive to cold. Simple vasospastic phenomena may be present rather than true Raynaud's phenomena.

It is not uncommon to see dilated capillaries or multiple areas of capillary hemorrhage scattered about through the skin and mucous membranes. These retain their red color and are not absorbed. Many patients appear to exhibit a loss of body hair, with a moderate increase of hair on the extremities.

The skeletal muscles may show varying degrees of atrophy and weakness. The atrophy may be symmetrical or unilateral, or it may be localized. The reflexes are usually normal. Any abnormal reflexes are usually due to constrictive changes in the skin and muscle, rather than to nerve lesions, except in the rare case with central nervous system involvement. Abdominal distention may be marked or may be limited by the rigidity of the skin.

Auscultation of the lungs may reveal roughening of the breath sounds, indicative of pulmonary fibrosis. The heart may be enlarged. Changes in rhythm, auricular fibrillation, or gallop rhythm may be heard. Murmurs

FIG. 3. Roentgenographic studies of a patient with sclerodactylia. Note the absorption of the terminal tufts and almost total disappearance of distal phalanges. Note the punched-out areas of the distal portion of the third metacarpal bone, left hand; destruction of phalangeal joints, and contracture deformities. Calcium deposits may be seen on the radial side of the wrist.

indicating involvement of the mitral valve may be heard, so that confusion with rheumatic fever sometimes occurs.

The mind is usually clear, but late in the disease the patient may complain of loss of memory, depression and diminished mental acuity.

LABORATORY FINDINGS

In general, the laboratory findings reflect the extent of organ or tissue involvement. There are no laboratory tests diagnostic of or specific to scleroderma.

Multiple serum calcium determinations in this series were normal. Two patients developed a hypercalcemia after parathyroidectomy. The blood

calcium had been normal prior to surgery. Inorganic phosphate determinations were all within normal limits. The phosphatase activity was also within normal limits. Chloride determinations were made on whole blood and were normal or slightly elevated. The total cholesterol concentrations in all cases were normal. The ratio of esterified cholesterol to the total cholesterol was also normal. The glucose content of the blood was within normal limits in practically all cases studied. One case in the entire series showed a hyperglycemia. This patient was a diabetic who was controlled by diet. Glucose tolerance tests were for the most part normal. Occasionally a diabetic curve was seen and, rarely, a hypoglycemic curve. Uric acid determinations were made on patients who had calcium deposits over joints. All were within normal limits. The urea nitrogen and nonprotein nitrogen, and their ratio, were within normal limits until renal failure developed. The total protein was normal in almost all cases, although there was a slight increase in the globulin content. In one patient there was a decrease in the total proteins and a reversal of the ratio. This patient had a pronounced nephrotic syndrome. A recent report on the electrophoresis of proteins in scleroderma [97] revealed a rise in globulin which was apparent chiefly in the gamma fraction. This is in agreement with studies by one of us.[105]

The cephalin-cholesterol flocculation tests were negative in two patients and positive in 10. Thymol turbidity tests were within normal limits in five patients and abnormal in eight. Bromsulphalein excretion was normal in these cases. Since none of our 12 cases autopsied revealed any changes in the liver, and since there are no reports of such changes, it would appear that these tests are indicative of some other phenomena. The positive flocculation tests are probably due to changes in the proteins, as has been demonstrated by Kobat et al.[106]

Vitamin A determinations were normal in 10 patients examined. Vitamin B determinations in six patients showed a decreased thiamin in two and absent riboflavin in four. The niacin content was normal in all six patients. Ascorbic acid concentrations of the serum and the five hour saturation test [35] were done on 48 patients. In 66 per cent a vitamin C deficiency was demonstrated.

No abnormalities were noted in the usual routine urine analyses early in the disease. Addis counts were usually within normal limits. An abnormal count was found in only six patients. These patients presented other evidence of renal damage.

Gastric analysis was normal in about 80 per cent of the patients examined.

In five cases the CO_2 combining power, and in six cases potassium, sodium and chlorides in the serum were determined and found to be within normal limits.

The basal metabolic rates were determined on 67 patients and were within normal limits in 53. Five patients had an increased rate, nine a

decreased rate. The range of the tests varied from minus 15 to plus 16 per cent. In the patient with a rate of plus 16 per cent there were no confirmatory signs of hyperthyroidism.

The hemoglobin, red blood cell, white blood cell and differential counts were within normal limits in all uncomplicated cases. One patient had an eosinophilia. Where an infection was present, the usual white blood cell response was noted. The erythrocyte sedimentation rate was elevated in 85 per cent of all of our cases. The change ranged from 5 to 60 mm. in one hour by the Westergren method.

All serologic blood tests for syphilis (Kahn, Mazzini or Wassermann) were negative on 150 patients. Three patients gave a history of having had a positive test in the past. These had been adequately treated. The luetic infection in these patients antedated the scleroderma by many years.

The spinal fluid was studied in three cases and found to be normal.

Excretion of 17 ketosteroids was measured in 12 patients. The excretion was below normal in three patients and normal in nine.

Electroencephalography was performed on 52 patients.[52] Twenty-eight of these showed abnormalities, seven showed slight changes (borderline), and 17 were reported as normal. The abnormal tracings did not follow any pattern but were indicative of changes in cortical activity. Five of the definitely abnormal tracings were in patients suffering from localized forms of scleroderma. In three instances of unilateral scleroderma, contralateral cerebral changes were noted on the electroencephalographic tracings.

The electroencephalograph has not yet assumed a position in the diagnosis of the diseases of the brain comparable to that of the electrocardiograph in the diagnosis of heart disease. It is, however, generally accepted as a valuable diagnostic aid in localizing lesions of the cerebral cortex. Normal patterns have been established due to the rhythm of the potential currents set up between a set pattern of electrodes. Only about 5 per cent of clinically normal individuals show abnormal graphs. If we allow a larger percentage because of our mixed age group, which includes some children, the percentage of abnormal curves probably would not exceed 10. The patients studied represented all types of scleroderma. There was not sufficient similarity of the abnormalities to establish any general pattern for scleroderma. Similarly, no definite pattern has yet been established in vascular disease of the brain. There have been reports of decreased alpha activity of the cortex in patients suffering from cerebral arteriosclerosis, but this alteration is neither constant nor established as of diagnostic significance.

Although it is impossible to draw conclusions from these findings in the 52 cases studied by the electroencephalograph, certain presumptions may be made. Abnormal tracings were found in a high percentage of the cases. Lesions in the brain have been observed as far back as 1898.[24] It is possible that the abnormal tracings may indicate vascular lesions in the cortex of these patients suffering from scleroderma. It is also possible that alterations of an undetermined chemical nature may be responsible for such ab-

normal activity. To date we have no positive autopsy findings to correlate with electroencephalographic findings.

Review by Systems

Skin: The skin over the hands and face usually shows the first changes. These consist of a marked sclerosis of the subcutaneous tissue. The skin cannot be picked up in folds and on the face the lines of expression disappear. Section of the skin (figure 4) shows marked changes. The epidermis is atrophied, and there may be increased pigmentation in the basal layer. The collagen tissue is increased in amount and the fibers are greatly thickened. The tissue is less cellular than normal and the strands appear homogeneous. The dermal appendages are usually absent. The small vessels may be dilated, and frequently show a slight inflammatory exudate around the vessels. They may show marked thickening of the walls.

Eye, Ear, Nose and Throat: Changes in the teeth have been reported by Stafne and Austin [102] and Rosenthal.[103] These consist of thickening of the peridental membrane. Histologic examination did not reveal any notable changes in the teeth extracted from three patients in our group. The buccal mucosa may be involved and sometimes the tongue. In our entire series, only one patient developed cataracts. These were thought to be of the senile type. Precocious cataracts, as reported by Agatston,[101] were not seen.

Lungs: The first description of pulmonary lesions in scleroderma is credited to Finlay [96] in 1889. Von Notthafft,[84] in 1898, noted the appearance of vascular lesions in the lungs. Matsui,[85] and later Masugi,[82] also noted changes in the pulmonary blood vessels.

In 1941, Murphy, Krainin and Gerson [58] described a case of scleroderma with roentgenologic evidence of marked pulmonary fibrosis. They stated that diffuse pulmonary fibrosis had been reported previously in only six cases. These were pathologic reports with no roentgenographic studies of the lungs. There were associated findings of varying amounts of pulmonary emphysema, which was in each case associated with hypertrophy and dilatation of the right ventricle of the heart. In the case reported by Murphy and his associates there was no evidence of enlargement of the heart.

In 1941, Linenthal and Talkov [54] reported three cases of pulmonary fibrosis detected by roentgenologic examination. Respiratory difficulty in these cases developed as rapidly as the evidence of fibrosis. All three patients died within three or four years of the onset of dyspnea, but no postmortem examinations were obtained.

Jackman [50] in 1943 described four cases interpreted as fibrosis of the lungs. The x-ray findings varied from fine to coarse strands and were most prominent in the lower portion of the lungs. Of the four cases which had roentgenographic evidence of pulmonary fibrosis, one was autopsied. Pathologic examination of the lungs showed diffuse pulmonary fibrosis.

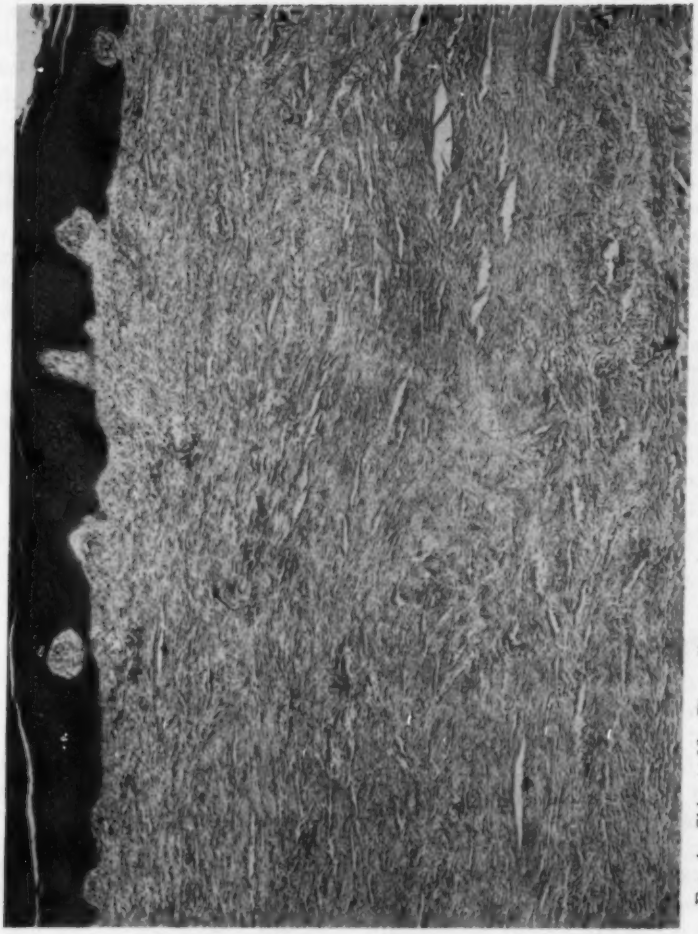


FIG. 4. Skin, × 85. The collagenous tissue is increased in amount. Dermal appendages are absent.

It is interesting to note that this case showed the least fibrosis on x-ray examination. We have had a similar experience. In the same year, Weiss, Stead, Warren and Bailey [72] also described these lesions in the lungs. In 1943, Pugh, Kvale and Margulis [87] reported a case of scleroderma with diffuse pulmonary fibrosis. Getzowa,[55] in 1945, and Dostrovsky,[94] in 1947, reported two cases of scleroderma with cystic and compact pulmonary sclerosis. These cases demonstrated far greater degenerative changes than had been previously described. The lungs were composed largely of connective tissue in which cystic degeneration had occurred. In our own series, 53 patients were examined radiographically. Eighteen were reported as normal. Twenty-seven patients were reported as having changes varying from root branch thickening to moderate pulmonary fibrosis. In one patient there were marked pulmonary fibrosis and calcification. In three patients there was a nodular type of fibrosis which extended along the roots and was more pronounced toward the base. These findings were confirmed at autopsy in 11 cases examined. Four patients had old apical lesions of tuberculosis.

Studies on two of our cases revealed a marked impairment of gaseous exchange in the lungs, one revealing only 56 per cent of normal transfer.

Physical examination of the lungs may be completely negative or show fine, moist râles. X-ray examination of the lungs may show several different lesions of fibrosis. These may consist of:

1. Extensive pulmonary fibrosis with or without calcinosis.
2. Fine fibrotic strands extending to the bases.
3. A nodular type of fibrosis, also extending toward the base of the lungs.

Histologic examination of the lungs, in addition to the vascular lesions, showed marked thickening of the alveolar membranes (figure 5). A terminal pneumonia was frequently seen.

Heart: Although lesions in the heart in scleroderma were described years ago, they received scant attention until Weiss and his co-workers [72] pointed out specific lesions of the myocardium which occur in this disease. Since then, similar lesions have been reported by Bevans,[70] Goetz [66] and others.[57, 68, 93, 109] The symptoms associated with this syndrome are mainly dyspnea on exertion and those referable to abnormalities in rhythm. Dyspnea is more frequently symptomatic of cardiac than of pulmonary involvement. It is difficult, in the presence of extensive pulmonary fibrosis, to calculate the relative rôle of these lesions, since the two are commonly concurrent. However, the onset of dyspnea is of grave prognostic importance. Physical examination of the heart reveals no finding specific for scleroderma. Murmurs and abnormalities of rhythm, suggestive of rheumatic heart disease, may dominate the picture, so that this diagnosis is sometimes suggested as a concomitant finding. Pericarditis or pericardial effusion is only rarely

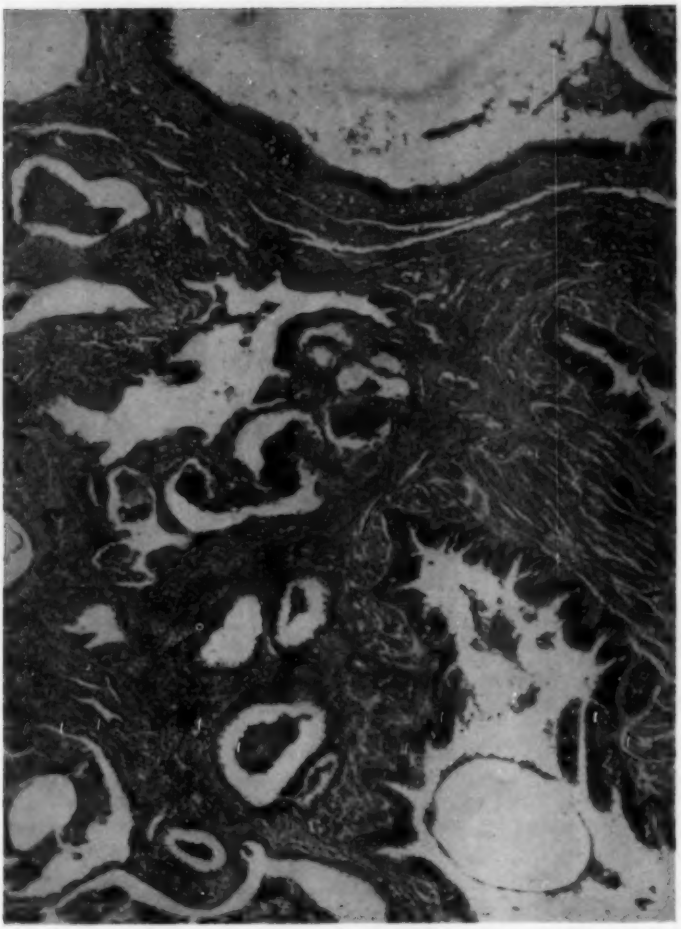


FIG. 5. Lung, × 160. Interstitial fibrosis and bronchiectasis.

present, if ever. The clinical diagnosis is dependent upon associated findings, namely, the changes in the skin and subcutaneous tissues.

Auricular fibrillation, gallop rhythm and slight prolongation of the Q-T interval may be noted in the electrocardiogram. Low voltage throughout the tracing, with axis deviation and slight intraventricular conduction defects, is more commonly seen. Five abnormal electrocardiograms were obtained on 51 patients examined (figure 6). Of the remaining 46 reported within normal limits, 20 showed minor changes of possible significance. X-ray visualization of the heart is also nonspecific.

The postmortem examination of the heart frequently reveals more pathologic change than is anticipated by examination of the heart prior to

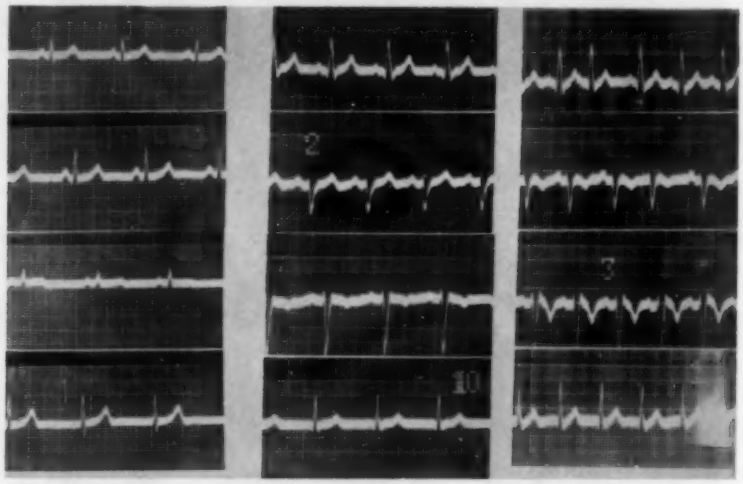


FIG. 6. Electrocardiograms taken on the patient in figure 1 over a period of five years, showing progressive changes.

death. We have found extensive changes in the myocardium with a normal electrocardiogram. Indeed, there were few patients who did not reveal some characteristic pathologic changes in the heart at post mortem, whether clinical signs were present or not.

We have found two main types of lesions. In one there is focal necrosis scattered through the myocardium in the midst of normal fibers (figure 7). In a second type, the muscle fibers are infiltrated with vascular connective tissue (figure 8). More widespread fibrosis has been reported. In some cases the area of fibrosis extended from the epicardium to the endocardium. As has been previously reported, these lesions were apparently independent of any changes in the nutrient vessels. It was not uncommon to find normal vessels amid areas of extensive fibrosis. Frequently the leaflets of the mitral valves show small nodules at their free margins. These nodules

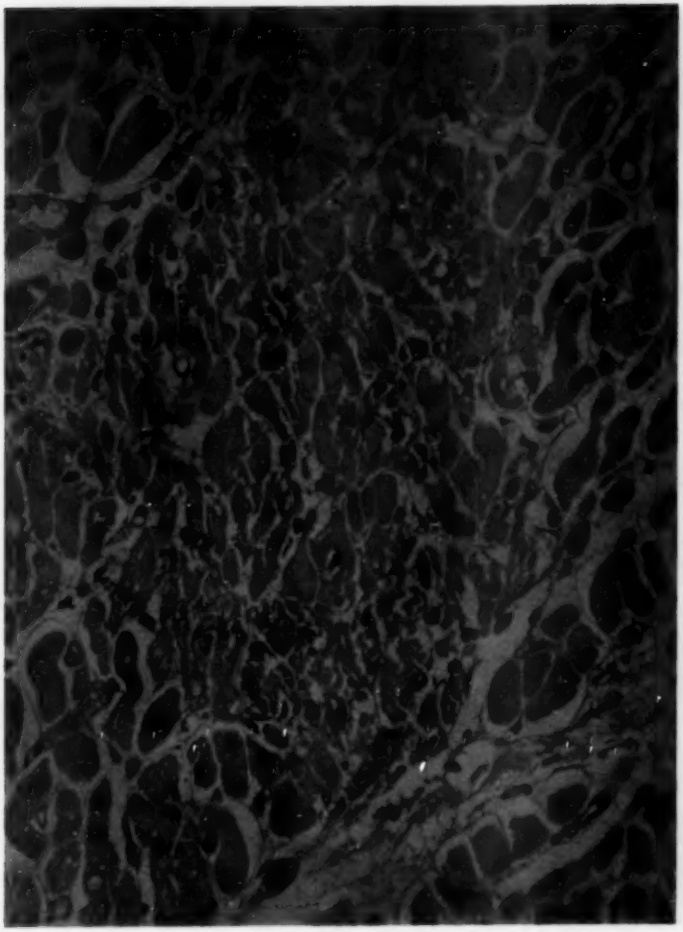


FIG. 7. Heart × 410. Focal necrosis of the myocardium.

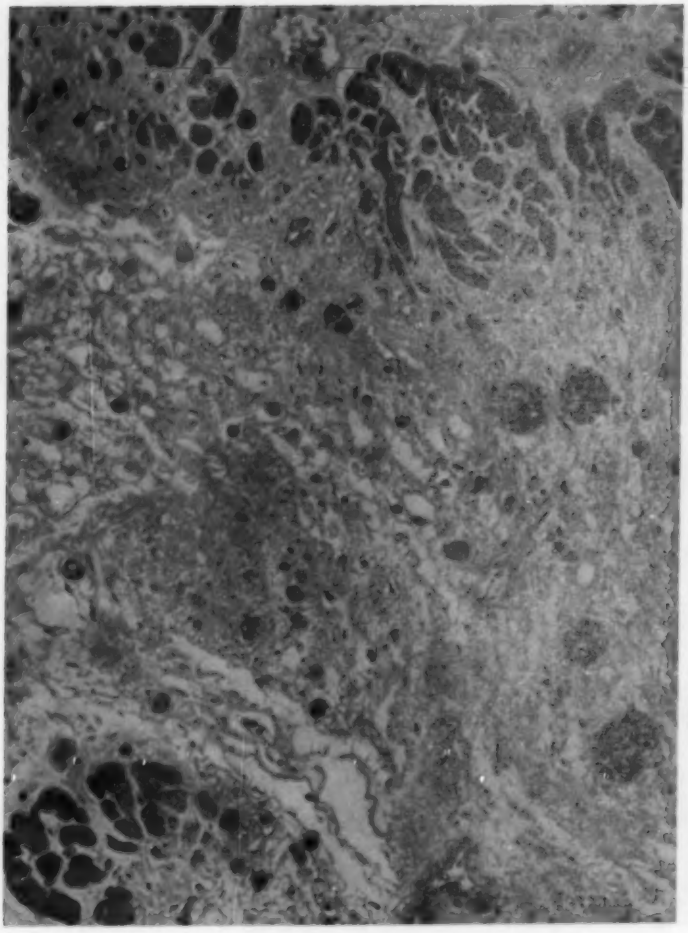


FIG. 8. Heart, × 216. Interstitial fibrosis of the myocardium.

are covered by endocardium. Changes in the mitral valve may produce what is clinically diagnosed as rheumatic heart disease. The coronary arteries are rarely involved. If cardiac failure is present, the response to digitalis is poor.

It is these lesions and those affecting the gastrointestinal tract which establish this as a disease of the connective tissues rather than as a vascular disease, in spite of the preponderance of the vascular symptoms.

FIG. 9. Kidneys, showing coarsely granular surface and cortical scarring.

Kidney: In the clinical picture of scleroderma there is little in the disease to call attention to the kidneys unless, or until, a terminal phase is reached. It has been reported that red blood cells in the urine are seen early in this disease.[56] We have not been able to confirm this finding. In fact, urinalysis and all kidney function tests are normal until the kidneys are so affected as to produce clinical signs of renal failure. Once this occurs, the confirmatory evidence of the laboratory becomes overwhelming, and the

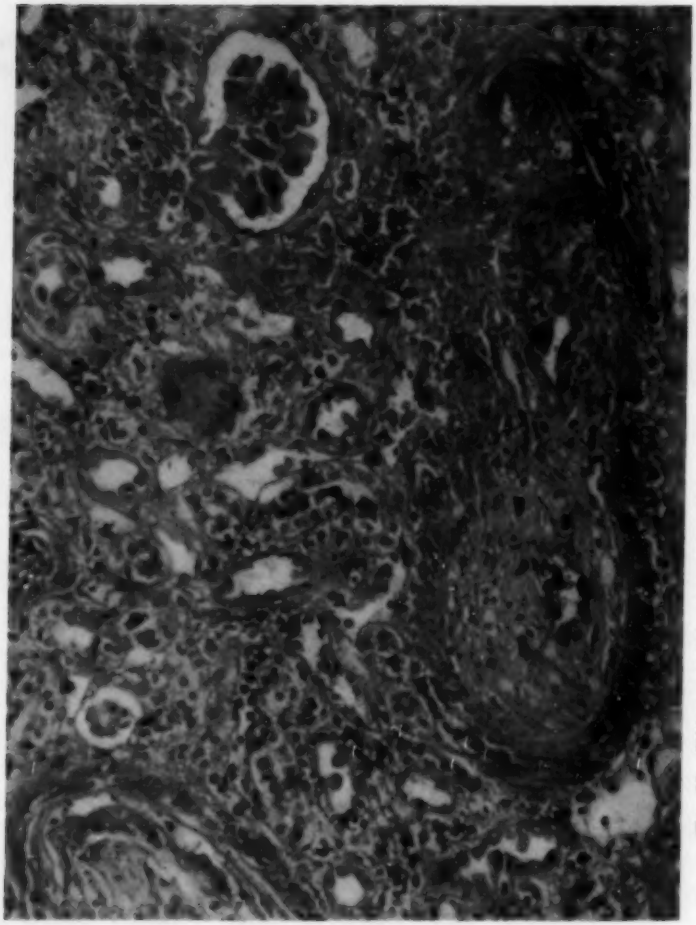


FIG. 10. Kidney, × 346. Arteritis, with intimal proliferation and partial occlusion.

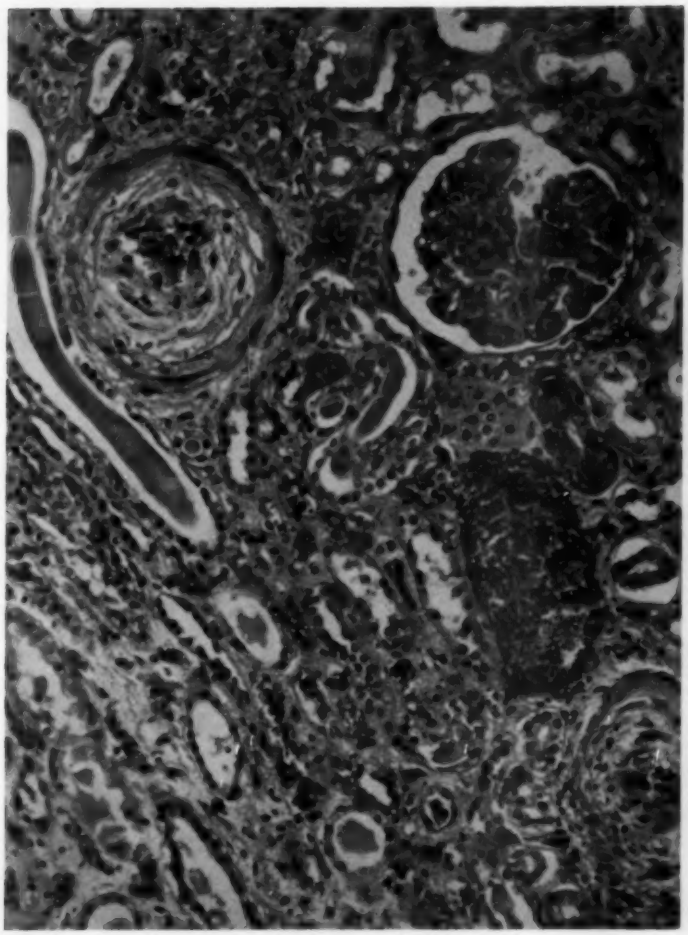


FIG. 11. Kidney, × 220. Intimal proliferation, with occlusion of small artery. Sclerosis of intraglomerular capillaries.

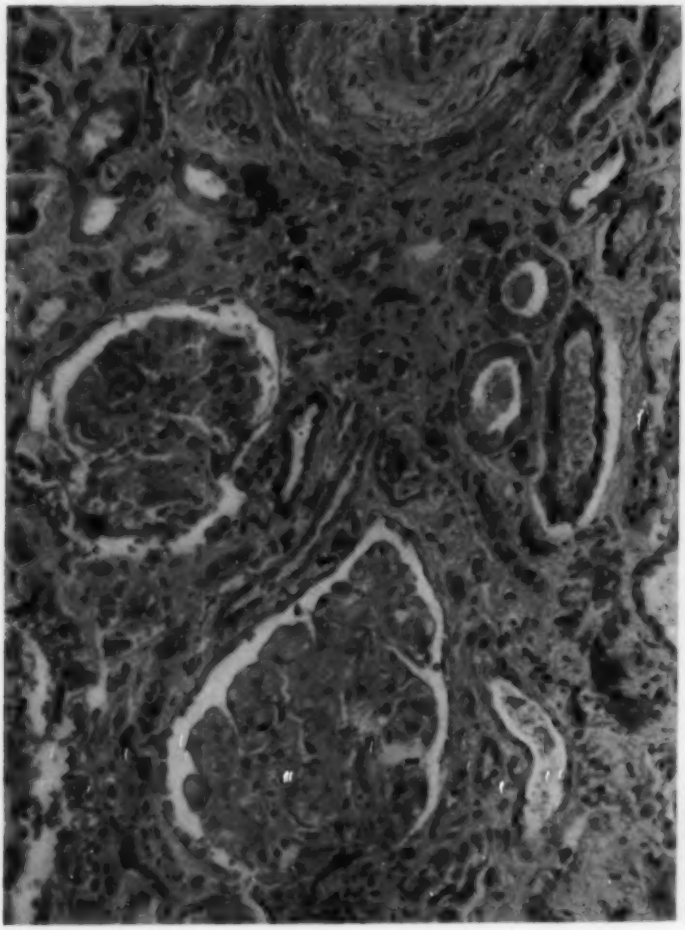


FIG. 12. Kidney, × 440. Sclerosis of glomerular capillaries. Intimal proliferation with occlusion of small artery (at edge of photograph).

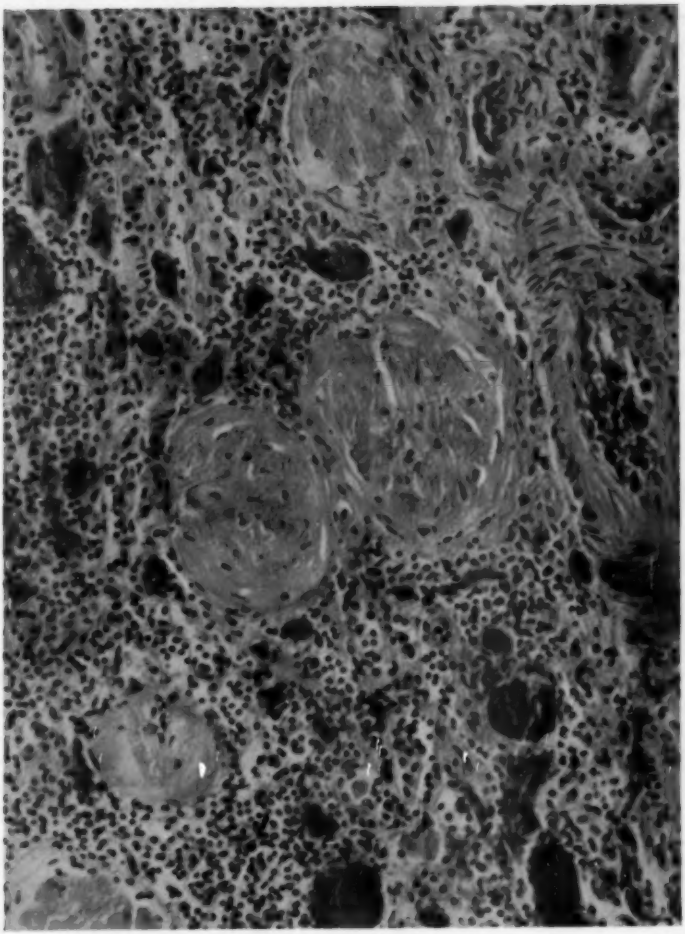


FIG. 13. Kidney, × 240. Fibrotic glomeruli in area of scarring.

course of the disease becomes very rapidly fatal. Previous reports, while presenting evidence of renal lesions, have not emphasized the fact that involvement of the kidney occurs in practically all cases. Recently some reports [107, 108, 109] have emphasized this finding.

The histologic findings were considerable. In all of the patients autopsied, pathologic findings were present in the kidneys. Changes varying considerably in severity and type may be seen. The kidney may have a coarsely granular surface with cortical scarring (figure 9), or it may show signs of infarction. The blood vessels may show various types of lesions. Two types predominate, acute arteritis and arteriosclerosis (figures 10, 11, 12). The vascular changes which accompany hypertension and arteriolar sclerosis may also be present. The smaller arteries as well as the arterioles are usually involved. Thrombosis may occur. The glomeruli may be entirely fibrotic (figure 13). The renal epithelium itself may be considerably affected.

In the clinical picture of the terminal phase, protein, red blood cells and casts are found in the urine. Retention of nitrogen in the blood and reversal of the albumin-globulin ratio, with occasional decrease of the total blood protein may occur. The blood pressure, which has hitherto been normal or below normal, becomes elevated. With these findings, associated changes in the fundi also appear.

There are usually no symptoms related to the urinary bladder. However, a section of the bladder is of interest because of the vascular lesion demonstrated (figure 14).

Adrenals: In the past there have been occasional instances reported of difficulty in the clinical differentiation of Addison's disease and scleroderma. This difficulty is even more pronounced where the muscles are prominently affected. The similarity of the pigmentation of the skin, weakness, malaise and gastrointestinal disturbance is very great. While the two diseases may appear to coexist, the association is very uncommon. Talbott found only one case,[7] confirmed by autopsy and reported by Lichtwitz. Barlow,[51] in 1939, reported a case of scleroderma associated with adrenal neoplasm.

Although the case reported by Talbot and his associates [7] was admitted with a presumptive diagnosis of Addison's disease, this was later discarded when at necropsy the glands were found to be normal. We had two patients who had changes in the adrenal glands at necropsy. In one case, cortical adenomata were reported. In another, there was narrowing of the cortex with scattered foci of degeneration. The lipid was concentrated in the band that occupied a mid-zonal part of the fascicular layer.

Gastrointestinal Tract, Esophagus: Ehrman [90] of Vienna, in 1903, first described progressive dysphagia and involvement of the esophagus in a case of scleroderma. We have found no reports on such observations from that time until 1931, when Rake [88] described gross and microscopic postmortem findings in a case of scleroderma in which constriction of the lower end of the esophagus had been described by the roentgenologist six years earlier.

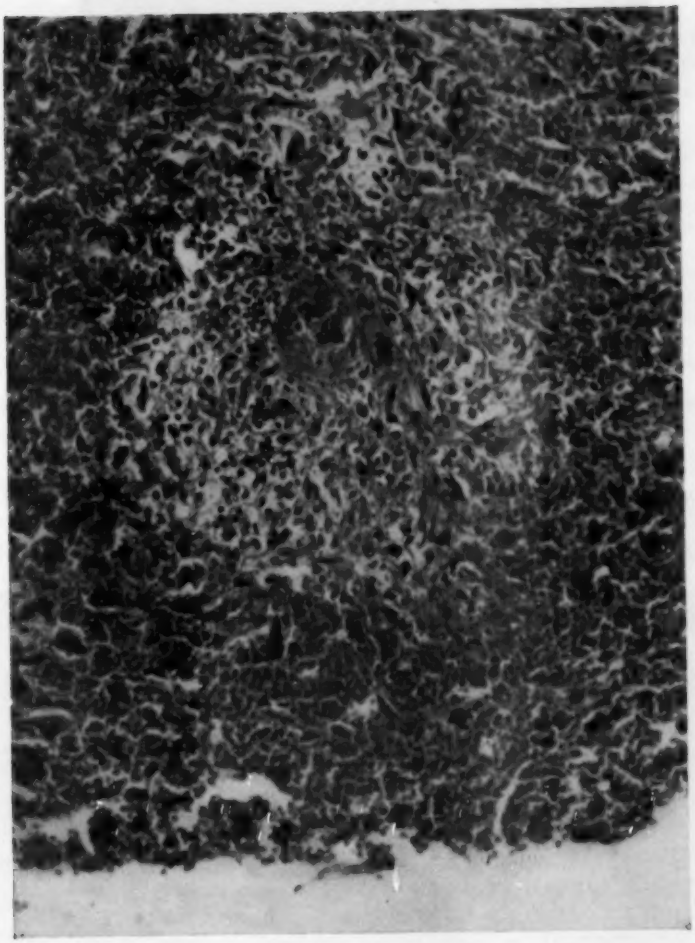


FIG. 14. Urinary bladder, × 190. Acute arteritis and periarteritis.

FIG. 15. Roentgenogram showing stricture of the lower third of the esophagus with dilatation above the stricture.

Later, Fessler and Pohl [91] and others [56, 57, 58, 59, 60, 63, 65, 66, 107, 108] described lesions of the esophagus associated with scleroderma.

The patient complains of difficulty in swallowing, usually first with solid food, and eventually with liquids. The dysphagia may be accompanied by vomiting. There may be merely a feeling of fullness or burning in the retrosternal or epigastric region, with no difficulty in swallowing. A patient may complain of a choking sensation on swallowing liquids or solids. Nausea is commonly present.

The symptoms are those due to a lack of motility throughout the gastrointestinal tract. A loss of smooth muscle may be found whenever these symptoms are present. The lack of contractibility accounts for the stasis

of the contents of the tract, producing the sensation of fullness and pressure. Analysis of the gastric contents reveals no abnormalities, since the secretory (or epithelial) portions are not primarily affected.

It should be remembered that the patient may experience difficulty due to improper mastication because of inability to open the mouth completely.

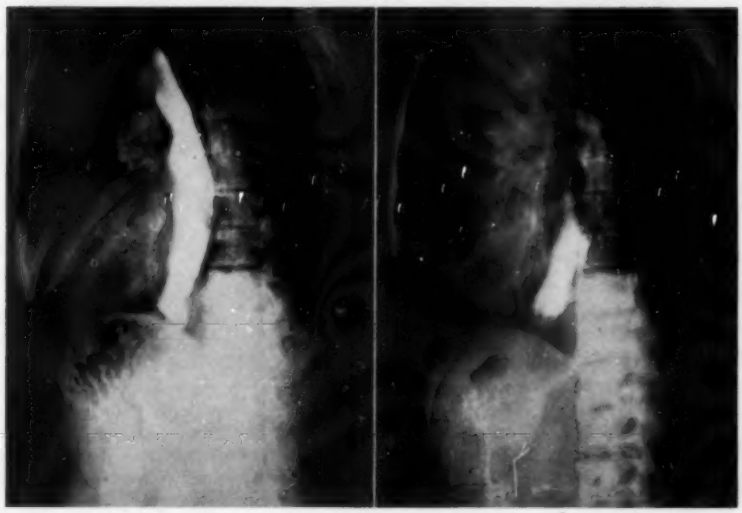
Roentgenologic study of the esophagus usually reveals three features which may be present individually or together:

a. *Constriction:* When this occurs, it is usually present in the lower third of the esophagus a few centimeters above the diaphragm (figure 15). This may sometimes be confused with the picture seen in cardiospasm. Scleroderma usually involves the lower third or half of the esophagus. In cardiospasm, it is only the cardia which is involved.

b. *Lack of Motility:* There is an increase in the time interval required for the passage of food or barium from the mouth to the stomach. The greatest delay in passage is noted at the cardia. Normal peristaltic movement may be absent altogether. There may be gaping, with a tendency for the barium meal to adhere to the walls of the esophagus. The emptying of the esophagus may depend almost entirely upon gravity.

c. *Dilatation:* The esophagus may be dilated, with some retardation of the passage at the cardia without complete obstruction. The barium may be retained above the cardia for many hours (figure 16 *a* and *b*).

In our series, seven of 14 patients who complained of dysphagia showed x-ray evidence of dilatation or stricture in the lower third of the esophagus. The changes which can be seen on esophagoscopy apparently vary only in



a *b*

FIG. 16. *a.* Barium in atonic dilated esophagus. *b.* Barium still present in the esophagus 4 hours later in the same patient.

degree. The appearance of the mucosa may be normal, it may be pale and smooth, or there may be severe induration and thickening, with broad and coarse mucosal folds. The point at which changes first appear is dependent, of course, upon the extent of the involvement. Most commonly, the first evidence is encountered in the middle third. A thick white exudate which can be easily separated from a granulating base, or whitish plaques resembling leukoplakia, may be seen. A stricture may be encountered after one passes the middle of the esophagus. This may be smooth, or, more commonly, superficial ulcerations are present.

Stomach: There have been no lesions reported in the stomach on roentgenologic or pathologic examination.

Small Intestines: Kraus,[56] in 1924, was apparently the first to report changes in the small intestine. Rake,[88] in 1931, Goetz and Rous,[93] in 1942, Hale and Schatzki,[60] in 1944, and Goetz,[66] in 1945, reported additional cases in which the small intestine was involved. These changes consisted of radiologic evidence of lack of peristaltic movement affecting the duodenum and jejunum, with localized dilatation of individual loops and breaking up of the barium. There is marked delay in emptying time of the loops involved. No changes of the mucosal pattern were noted. The picture of atony of the bowel predominates.

Colon: Examination of the large bowel by means of barium enema shows the barium to move more slowly than usual from the rectum to the splenic flexure. The colon may show areas of rigidity and peculiar narrowing, with areas of sacculation. There may be tendency toward sacculation without rigidity. The x-ray picture may be similar to that seen in ulcerative colitis. The large intestine may show merely those findings associated with an atony of the bowel, such as dilatation and distention, with incomplete contraction after evacuation of the barium. Sigmoidoscopic examination is usually negative.

Other Viscera: Some interesting arterial lesions were seen in the gallbladder (figure 17) and spleen (figure 18).

Blood Vessels: In our cases three types of lesions were seen:

a. Acute or subacute arteritis with cellular infiltration of all the coats of the blood vessels and the surrounding tissues (figure 14, 17). This may be accompanied by intimal proliferation.

b. More or less complete obliteration of the lumen due to intimal proliferation without cellular infiltration. This may represent a more advanced stage of the first type, or possibly a healing of the acute type (figures 10, 11).

c. An arteriosclerotic lesion in the kidney, possibly the result of hypertension. This type of lesion is frequently seen in the kidney in patients with hypertension and cannot be considered as a specific result of scleroderma (figures 11, 12, 13). However, the vessels affected are usually of a larger caliber than those involved in essential hypertension, where the arterioles are chiefly involved. Usually, the smaller arteries are affected as well as the arterioles.

From the published reports it appears that the smaller arteries are chiefly affected. Of the larger arteries, those occasionally involved are the digital, coronary and cerebral arteries. Changes in the renal and carotid arteries and the aorta are not commonly seen.

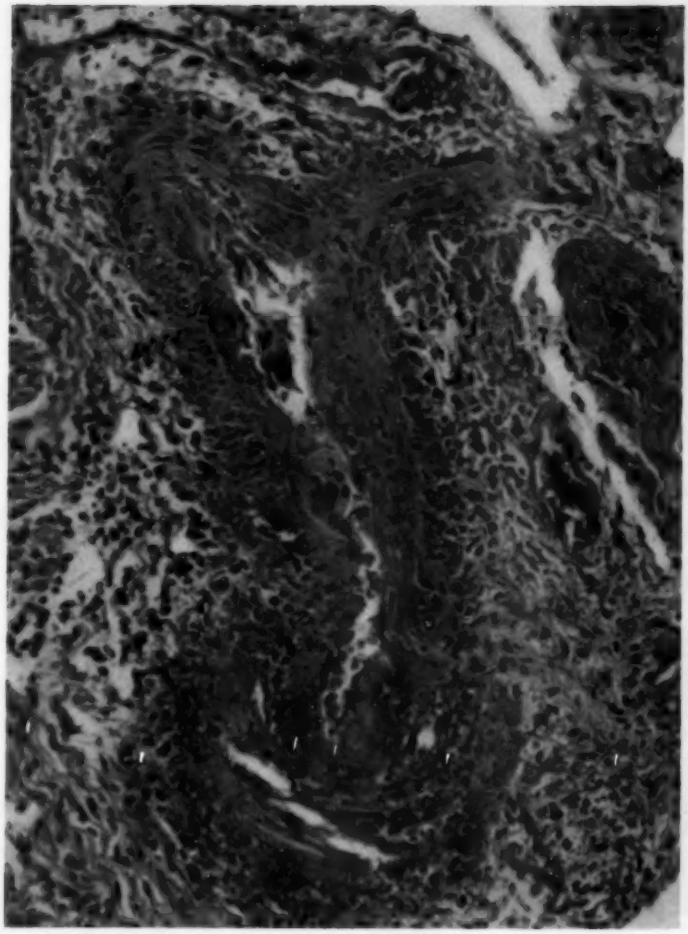


Fig. 17. Gall-bladder, × 240. Acute arteritis and periarteritis in peritoneal tissue.

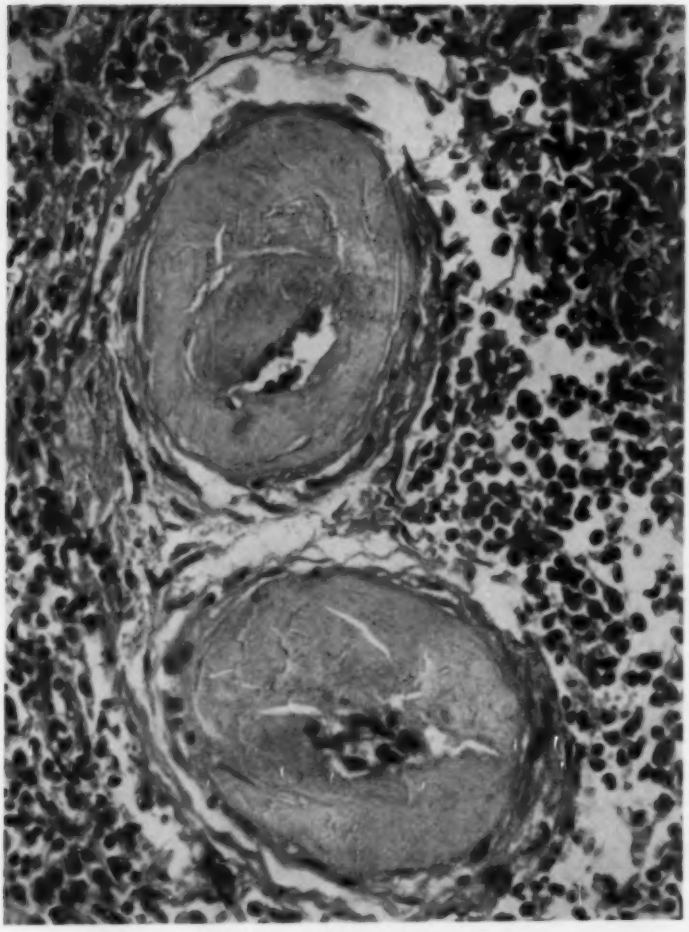


FIG. 18. Spleen, × 485. Sclerosis of splenic arterioles.

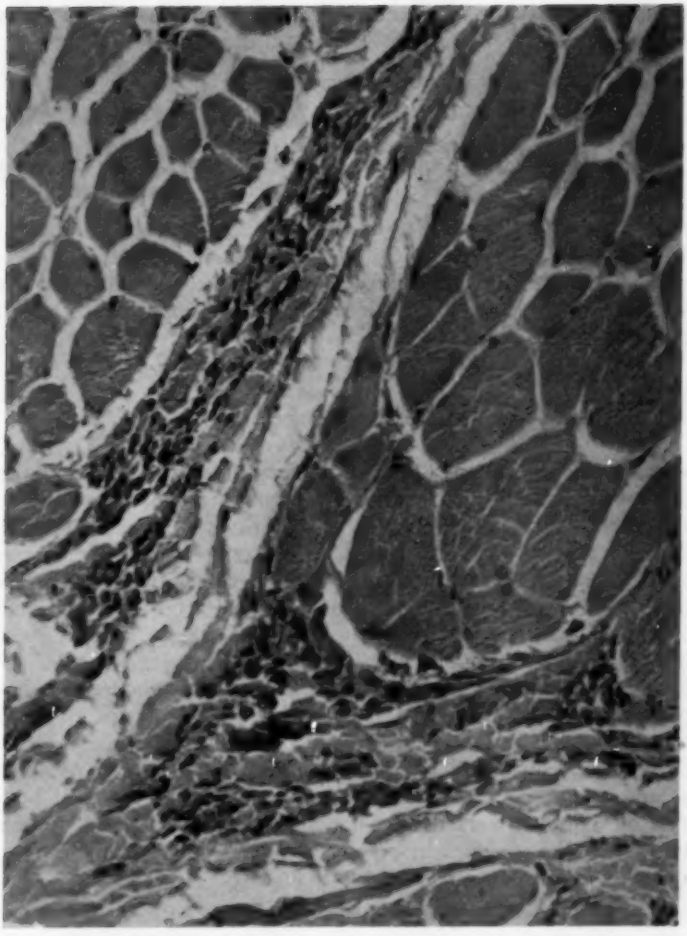


FIG. 19. Psoas muscle, × 250. Interstitial inflammatory infiltration between muscle bundles.

Skeletal Muscles: Atrophy of muscles is common. An interstitial inflammatory infiltration is of interest (figure 19). The picture is practically identical with that seen in dermatomyositis.

Summary of Pathology: In general, the lesions seen in scleroderma are of three types:

1. Changes in collagen in various parts of the body.
2. Changes described in the arteries, particularly of the acute type (arteritis).
3. Immediate and remote results of these lesions, comprising such changes as fibrosis, parenchymatous degeneration, infarction, etc.

Etiology

In considering the etiology of this disease, the theories which have been proposed in the past may be divided into four main groups:

1. Endocrine dysfunctions.
2. Nervous system disturbances.
3. Toxins, infections and trauma.
4. Vascular disease.

Endocrine Dysfunctions: The entire endocrine system, in whole or in part, has been accused at various times and by various authors as an etiologic factor in scleroderma. Hyperfunction of the thyroid has been blamed as frequently as hypofunction. In the large series reported by O'Leary and Nomland [11] there were no cases of diffuse scleroderma with a basal metabolic rate below normal. In seven cases there was evidence of hyperthyroidism and, in one, typical exophthalmic goiter. Leriche et al.[12, 13, 14] were the first to call attention to parathyroid dysfunction as an etiologic factor. They favored the thesis that dysfunction of these glands produces a skeletal osteolysis which in turn is followed by deposition of calcium in the skin. Bernheim and Garlock,[15, 16] in a series of 17 cases, offered as further evidence hyperplasia, hypertrophy and inflammatory changes in the parathyroid glands removed at operations. However, this was not a constant finding, and at a later date they retracted this hypothesis.[17] Ochsner and DeBakey [18] reported three cases in which they performed parathyroidectomy.

In hyperparathyroidism one expects to find:

1. Hypercalcemia and hypercalciuria.
2. Hypophosphatemia.
3. Negative calcium balance.
4. Skeletal decalcification.

In very few of the cases reported were a hypercalcemia and hypophosphatemia noted. Moreover, many investigators did not include these studies. Leriche, Jung, and DeBakey [12, 13, 14] point out that, in experimental chronic hyperparathyroidism, the blood calcium is at first increased but

within several months returns to normal and remains so. We have no information as to whether this is true in hyperparathyroidism in humans. We have found but two reported cases of carefully studied calcium balance in scleroderma. Cornbleet and Struck,[19] in reporting these two cases, pointed out that less calcium was excreted than was ingested. The reverse is true in hyperparathyroidism.

Generalized skeletal decalcification has been described in a few cases. In one case where it was described clinically, it was not found at necropsy.[7] However, decalcification does take place frequently in the bones of the hands and feet.

Selye [20] produced skin changes closely resembling those occurring in scleroderma by the intraperitoneal injection of parathyroid extract in young rats. His findings were confirmed by others.[14] Leriche and his co-workers [14] noted that the calcium content of the skin of these animals was increased to two and three times the normal. Such changes could not be produced in adult rats. The calcium content of the skin of humans with scleroderma is also increased.[100]

Perez [21] and others have reported clinical improvement following the use of dihydrotachysterol in a group of patients suffering from scleroderma. It is possible that such glandular dysfunctions are the result of the disease when it involves the parathyroid gland. Disturbances in adrenal function have also been reported [51] as possibly associated with this disease.

Disturbances in the Nervous System: Scleroderma has been considered by many as a neurotrophic disease. The following observations have been offered to support such contentions:

a. In most cases there is a symmetry of the lesions.
b. There is evidence of vasomotor instability:
Raynaud's syndrome is a frequent associated finding.
The onset is frequently at the menopause, a period when vasomotor changes are marked.
There is evidence of vasomotor or sympathetic nervous system disturbances producing visceral dysfunction in many of these patients.
c. There have been reports of beneficial results with the interruption of the of the sympathetic pathways by:
Sympathectomy.[12, 15, 16, 18, 22, 102]
Acetyl beta methylcholine chloride.[29]
d. There have been reports of scleroderma associated with:
Facial hemiatrophy.[11, 74]
Complete hemiatrophy.[23, 24]
Cerebral lesion.[25]
Changes in the spinal fluid and histologic changes in the central nervous system.[26]
e. The presence of electroencephalographic abnormalities.[52]

Toxins, Infections and Trauma: Scleroderma has been reported following syphilis, measles, tonsillitis, scarlet fever, diphtheria, pneumonia and influenza.[9, 11, 26] There are several reports of the occurrence of scleroderma following arsenic poisoning.[27, 28] Direct trauma to the skin, nerves or blood

vessels has been mentioned as a possible causative factor of this disease.[29] More recently an acid-fast bacillus, the sclerobacillus Wuerthele-Caspe,[99] has been suggested as the cause of scleroderma.

Vascular Disturbances:

a. Nearly all investigators report vascular changes as part of the pathologic picture of scleroderma. Lewis [4] and Landis [30] observed that most of the cases had an associated Raynaud's syndrome, and believed that the skin changes were secondary to this disease. In most of their reported cases the Raynaud's syndrome had been present for some time before the onset of the skin changes. In a report from this clinic [29] in 1937, 33 of 34 cases reported had associated vasospasm.

b. Reports of histologic studies have frequently noted a perivascular cellular reaction with secondary changes in the vessels, often obliterating them.

c. The capillaries of the nail-bed in cases of sclerodactylia have been reported as abnormal.[11, 31] Whether these changes were due to the accompanying Raynaud's syndrome or were a part of the sclerodermatous process was never clearly determined.

d. The injection of histamine into the skin of patients suffering from scleroderma produces wheals similar to those found in occlusive vascular disease. As these tests are performed there is a diminution of the size of the wheal formation in skin areas with impaired vascular supply. Finally, one finds an increasing number of reports of vascular changes in the viscera.[7, 8, 22, 23]

Types of Scleroderma

Scleroderma may be divided into two main types, a circumscribed and a diffuse. Further division of the diffuse type is without purpose or basis. The absence or presence of vasospastic phenomena preceding the onset of scleroderma has no relationship to the prognosis. It is possible that the presence of vasospastic phenomena with scleroderma may intensify the disease; it is certainly true that it intensifies the symptoms. The association does not appear to be essential in the production of the terminal phase.

It is difficult to associate as malignant a disease as the diffuse type with the relatively benign circumscribed type. We have avoided the designation of "localized," since it is possible in some patients to demonstrate lesions elsewhere than in the skin. We have been able to demonstrate gastrointestinal involvement, such as is sometimes seen in the generalized disease, in a patient with circumscribed lesions on the back and a small lesion on the jaw. It is this phenomenon, actually, which establishes this form as true scleroderma. Perhaps a more appropriate terminology would be "focal." In regard to the general designation of scleroderma we concur with the suggestion of Goetz, that systemic sclerosis is much more descriptive and anatomically more inclusive.

The term acrosclerosis, combining Raynaud's syndrome with scleroderma of the distal parts of the extremities, the face and the neck, was suggested by Hutchinson [41] in 1896. It has been reviewed and emphasized by Sellei.[87] Other investigators,[27, 88] chiefly O'Leary,[37] have stressed the di-

vision principally from the standpoint of prognosis. We do not believe that such a division is justified, since the basic pathology and the course are the same. Although some cases of so-called acrosclerosis are arrested, the same is true of some cases of diffuse scleroderma. Raynaud's phenomena frequently appear with or after the onset of sclerodermic changes. Several of the autopsies in our series were on patients who could have been classified as cases of acrosclerosis. This is also true of reports by others.[66, 70] Visceral symptoms in this group are not less common than in generalized scleroderma.

Scleroderma and Pregnancy

In our series we had two cases of pregnancy in the course of this disease. We had two other patients in whom a Raynaud's syndrome appeared about the fifth month of pregnancy. There was normal spontaneous delivery in both. Skin changes appeared about two months after term. One of the patients became pregnant again without any complication except that she delivered a stillborn infant at term. We had one other patient who developed vasospastic phenomena during her first pregnancy two and one-half years ago. She went to term but delivered a stillborn child. She became pregnant again after developing all of the skin changes of generalized scleroderma. This time, she delivered prematurely an infant of about six months who died a few hours after delivery. An autopsy was performed in both instances, but no findings directly related to scleroderma were noted. There is one other report [61] of pregnancy in an advanced case of generalized scleroderma. This patient delivered a normal infant about six weeks prematurely. During the prenatal period the condition remained static. After delivery the lesions again became progressive. The patient died about six years after delivery because of an intestinal obstruction due to scleroderma. The child remained completely normal. In six of our patients the first symptoms of the disease appeared shortly after delivery. It is possible in several cases that this disease had been present in a mild form when conception took place, but we cannot state its positive existence except in the two previously mentioned.

We have been informed of another patient who became pregnant during the course of this disease. In her case a therapeutic abortion was performed because of the severity of the scleroderma. The low incidence of pregnancies in a group of women of the child-bearing age cannot be denied in the presence of continued usual sexual relations. The rarity of pregnancy therefore suggests that there is decreased fertility but not complete sterility in this disease.

Calcinosis

The normal process of calcium deposition is termed calcification. Many authors applied the term calcification to all forms of calcium deposition. Some have expressed the opinion that normal calcium deposition should be

termed ossification, and that abnormal calcium deposition should be termed calcification. However, the most common term for the deposition of calcium in the skin and soft tissues appears to be calcinosis. Many types of calcinosis have been described, but only those in relation to scleroderma will be discussed.

In 1878, Weber [40] reported the first cases of calcinosis associated with scleroderma. He interpreted this condition as a form of gout. In 1895, Lewin and Heller [78] reviewed 507 reported cases of scleroderma, of which six were associated with calcinosis. In 1919, Jadassohn [100] showed by histologic methods that calcium is deposited diffusely in the corium between the collagen fibrils. This observation was confirmed by chemical analysis, which showed that sclerodermatous skin contains more calcium than normal skin. The work of Cornbleet and Struck [19] was in complete accord. Thibierge and Weissenbach [76] in 1911 reported nine cases in which calcinosis and scleroderma were associated. Durham [28] in 1928 added 14 more cases. He stated that the association of these two conditions was more than incidental. Since then, several other cases [20, 73, 74, 79] have been reported. In our own series, the association of calcinosis with scleroderma was at least 10 per cent.

At least 10 types of calcinosis have been described, depending primarily on the site of the calcium deposition and the disease associated, if one is present. For simplicity, let us assume that the term calcinosis denotes the deposition of calcium in greater or lesser amounts in the skin and/or subcutaneous tissues.

In scleroderma, the calcinosis is generally found in the extremities, most commonly about the phalangeal joints (figures 2, 3). Calcium deposits may ulcerate through the skin, releasing a chalky material. Calcium deposits may also be seen in the soft tissues without ulceration. X-rays of portions of the body which are apparently not involved may reveal abnormal calcium deposits, even though there are no symptoms or physical findings to suggest their presence.

There have been many speculations regarding the reason for calcinosis. Among the numerous etiologic factors given have been local trauma, cold, interference with blood supply producing local vascular degeneration, disturbance in metabolism and inadequate nutrition. Generally, two theories are implied. The first is that there is a primary alteration in calcium metabolism; the second, that calcium is deposited in previously degenerated tissue. Neither theory has been conclusively demonstrated. It has been recognized that calcification frequently follows inflammation and degeneration of adipose tissue. Bauer, Marble and Bennett [80] showed that, although calcification usually occurs in tissues that are dead or in a condition of reduced vitality, fatty degeneration frequently precedes the calcification. The initial histologic change in this type of cutaneous calcinosis consists of a deposition of fine granules of calcium salts around the periphery of fat cells, which otherwise appear histologically normal. The disease progresses

until calcium has been deposited within the fat cells and eventually replaces whole fat lobules. They maintain that the conditions under consideration were metabolic in origin, in spite of the normal values for blood calcium and phosphorus obtained in balance studies.

There is undoubtedly some alteration in calcium metabolism present in this disease, since the calcium content of the skin itself is increased and so many patients have, in addition, deposition of calcium in other areas. Whether this alteration in calcium metabolism is concerned with the changes in the collagen substance or is itself a part of this change is not known.

Course of the Disease

The course of the disease cannot be said to follow any particular pattern for all cases, even when the outcome is fatal. The picture that the patient presents when first seen by the physician, whether the lesion be localized or generalized, may remain unaltered during life. Complete resolution is rarely seen in the generalized type and, when it occurs, the diagnosis of scleroderma is questionable. As the disease progresses the complaints become indicative of visceral involvement, and the various physical findings and laboratory examinations confirm the symptoms. These were discussed in the individual sections of this paper. Roentgenologic examination often presents evidence of the disease in the absence of physical findings. Similarly, postmortem examination may reveal extensive lesions in the absence of clinical signs. Dysphagia may be present for some time and, in the absence of stricture, may disappear. However in most cases, symptoms of visceral involvement remain until death. In spite of pulmonary fibrosis, the onset of dyspnea does not usually occur until cardiac involvement is present. Dyspnea, therefore, is a grave prognostic sign and usually heralds the onset of the terminal phase. The response to digitalis is poor. The kidneys are nearly always involved in the final phase, as noted by the appearance of red blood cells, casts and protein in the urine. Decreased kidney function is confirmed by decreased urea clearance, retention of nitrogen in the blood and inability to concentrate the urine. Hypertension is usually associated with involvement of the kidneys. Examination of the fundi reveals the typical findings of hypertensive retinitis. Occasionally, intestinal obstruction may be the final result of the gastrointestinal lesions.

In summary, one may state that this is a disease of the connective tissue of unknown etiology. Because the connective tissue is derived from mesenchyme, as are smooth muscle, endothelium and mesothelium, these other tissues are commonly involved wherever they may be located.

Treatment

The treatment of the disease has been very unsatisfactory. In the past 14 years we have used all of the recommended medications. AT 10 (Hytakerol), vitamins D and E, protein hydrolysate, Promin, Priscoline,

Etamon, typhoid vaccine, Mecholyl, para-aminobenzoic acid and sympathectomy have been used, without success. These patients, like so many others with disease of the mesenchyme, can achieve a status quo for varying periods of time. This may occur coincidentally with the institution of some medication which results in a favorable report. It should be noted that none of these favorable reports has followed long-term observation of any sizable group of patients.

Recently we have had the opportunity of using Cortone * in eight patients for a period of from several months to almost four years. Two of these patients had hypertension with congestive failure. One of them had developed chronic auricular fibrillation. With treatment all improved despite the most severe deformities. One was given 300 mg. of Cortone in divided doses daily until definite improvement was noted. Then she was given 200 mg. daily for four weeks, followed by 100 mg. daily for seven weeks. She has since been maintained on 100 mg. every other day. She had a drop in blood pressure from 200/100 mm. of Hg on admission to 90/60 mm. of Hg on discharge. At her last visit to the clinic her blood pressure was 120/80 mm. of Hg. She has been on continuous therapy for over four years. The other patient with auricular fibrillation, congestive failure and hypertension received the same type of treatment except that she was started and kept on 200 mg. daily. Her general condition was much improved and, although she was still fibrillating and had hypertension, she became much more active. Her edema and dyspnea all but disappeared. In our experience with these patients the edema due to congestive failure may be easily controlled by the use of mercurials in proper amounts. Treatment in this patient was stopped after three months due to an acute depression, which had existed previously to a lesser degree. In two patients an attempt was made to stop medication. In both there was a return of symptoms. We intend to continue these patients on maintenance doses indefinitely. Although our series is small at present, we selected the most severe cases so that we could have more objective criteria upon which to judge improvement. All but one patient showed objective improvement. All but one of these patients are still alive and ambulatory today, although a fatal outcome was expected in at least 50 per cent of these cases without cortisone. The patient who died had discontinued her treatment against advice.

In our experience, there is no doubt that in adequate doses this is the only therapeutic agent available at the present time which offers any hope to the patient with rapidly advancing disease. We have had no experience regarding the use of adrenocorticotropic hormone (ACTH) in this disease.

Even with the adrenal cortical hormones one must not overlook proper nutrition and physical therapy as important adjuncts in the rehabilitation of patients with this disease. If these hormones are not readily available, there is little to offer these patients which differs from the routine employed in rheumatoid arthritis or other allied diseases.

* Cortone has been supplied by Merck & Co.

Summary and Conclusions

1. Scleroderma is a disease of the mesenchyme of unknown etiology.

2. The symptoms and findings vary according to the location of the tissue involved, and may be limited or very extensive.

3. Due to the widespread involvement of the arteries, in only a very few cases are the lesions limited to one system of the body.

4. This disease may be fulminating in type, becoming rapidly fatal, or may remain in an arrested state throughout a normal life span. Its course is usually episodic, with variable periods of arrest and exacerbation.

5. There is no curative therapy. However, in a limited number of severe cases cortisone appears to have arrested the progress of the disease. It has been used continuously in one of our patients for over four years.

BIBLIOGRAPHY

1. Curzio: Dissertations anatomique et pratique sur une maladie de la peau d'une espece fort rare et fort singuliere, No. 23, 1752.
2. Griffiths, W. J.: Biochemical aspects of dermatomyositis, Brit. J. Dermat. **52**: 295, 1940.
3. Freudenthal, W.: Generalized scleroderma and dermatomyositis: a histological comparison, Brit. J. Dermat. **52**: 289, 1940.
4. Lewis, T.: Notes on scleroderma (dermatomyositis), Brit. J. Dermat. **52**: 233, 1940.
5. Dowling, G. B.: Generalized scleroderma, Brit. J. Dermat. **52**: 333, 1940.
6. Dowling, G. B., and Griffiths, W. J.: Dermatomyositis and progressive scleroderma, Lancet **1**: 1424, 1939.
7. Talbot, J. H., Gall, E. A., Consolazio, W. V., and Coombs, F. S.: Dermatomyositis with scleroderma, calcinosis and renal endarteritis associated with focal cortical necrosis, Arch. Int. Med. **63**: 476, 1939.
8. Banks, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosis, the Libman-Sacks syndrome and polyarteritis nodosa? New England J. Med. **225**: 433, 1941.
9. Boardman, W. P.: Scleroderma, with special reference to its etiology and treatment, Arch. Dermat. and Syph. **19**: 901, 1929.
10. Burch, G. E.: Scleroderma: Etiology and abnormal physiology, New Orleans M. and S. J. **92**: 12, 1939.
11. O'Leary, P. A., and Nomland, R.: A clinical study of one hundred and three cases of scleroderma, Am. J. M. Sc. **180**: 95, 1930.
12. Leriche, R., and Jung, A.: Recherche sur la nature de la sclerodermie. Les traductions tissulaires de l'hyperparathyroidism dans la sclerodermie, Presse méd. **43**: 1361, 1935.
13. Leriche, R., Jung, A., and DeBakey, M. M.: The surgical treatment of scleroderma. Rationale of sympathectomy and parathyroidectomy, Surgery **1**: 6, 1937.
14. Leriche, R., Jung, A., and Sureyya, C.: La peau dans l'hyperparathyroidism experimental, etude de la sclerodermie experimentale, Presse méd. **43**: 777, 1935.
15. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's disease and scleroderma, Ann. Surg. **101**: 1012, 1935.
16. Garlock, J. H.: Parathyroidectomy for Raynaud's disease and scleroderma, S. Clin. North America **16**: 771, 1936.
17. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's disease and scleroderma (late results), Arch. Surg. **38**: 543, 1939.
18. Ochsner, A., and DeBakey, M.: Surgical considerations of scleroderma, New Orleans M. and S. J. **92**: 24, 1939.

19. Cornbleet, T., and Struck, H. C.: Calcium metabolism in scleroderma, Arch. Dermat. and Syph. **35**: 188, 1937.
20. Selye, H.: A condition simulating human scleroderma in rats injected with parathyroid hormone, J. A. M. A. **99**: 108, 1932.
21. Perez, W. M., Soffer, L. S., and Silbert, S.: Improvement in two cases of diffuse scleroderma by the use of Dihydrotachysterol (A.T. 10), J. Mt. Sinai Hosp. **6**: 333, 1940.
22. Adson, A. W., O'Leary, P. A., and Brown, G. E.: Surgical treatment of vasospastic types of scleroderma by the resection of sympathetic ganglia and trunks, Ann. Int. Med. **4**: 555, 1930.
23. McCracken, R. H.: Scleroderma. Report of a case with scleroderma and hemiatrophy, J. Pediat. **9**: 173, 1936.
24. Steven, J. L.: Case of scleroderma with pronounced hemiatrophy of the face, body and extremities—death from ovarian tumor—account of the postmortem examination: a sequel, Glasgow M. J. **50**: 401, 1898.
25. Petraceck, E., and Pitka, V.: Unilateral scleroderma with signs of cerebral lesion, Ceska derm. **17**: 251, 1937.
26. Murray-Will, E.: Scleroderma and syphilis, Brit. J. Dermat. **9**: 187, 1924.
27. Moench, L. M.: A case of chronic arsenic poisoning in a child associated with profound anemia and scleroderma, New York State J. Med. **36**: 1029, 1936.
28. Ayres, S., Jr.: Scleroderma as a possible manifestation of chronic arsenic poisoning, Arch. Dermat. and Syph. **2**: 747, 1920.
29. Duryee, A. W., and Wright, I. S.: The treatment of scleroderma by means of acetyl beta methyl chloride (Mecholyl) iontophoresis, Am. Heart J. **14**: 603, 1937.
30. Lewis, T., and Landis, E. M.: Further observations upon a variety of Raynaud's disease with special reference to arteriolar defects and to scleroderma, Heart **15**: 330, 1929–31.
31. Brown, G. E., and O'Leary, P. A.: Skin capillaries in scleroderma, Arch. Int. Med. **36**: 73, 1925.
32. Masugi, M., and Ya, S.: Diffuse scleroderma and its vascular changes, Virchows Arch. f. path. Anat. **302**: 39, 1938.
33. Weidman, F. D.: Necropsy findings in a case of congenital scleroderma and sclerodactylia, Arch. Dermat. and Syph. **1**: 375, 1920.
34. Osler, W.: On diffuse scleroderma with special reference to diagnosis and to the use of thyroid gland extract, J. Cut. and Genito-urinary Dis. **16**: 127, 1898.
35. Wright, I. S., Lilienfeld, A., and MacLanathen, E.: Determination of vitamin C saturation, Arch. Int. Med. **60**: 264, 1937.
36. Clinicopathological Conferences New York Post-Graduate Hospital: Case report, New York State J. Med. **41**: 1870, 1941.
37. O'Leary, P. A., and Waisman, M.: Acrosclerosis, Proc. Staff Meet., Mayo Clin. **15**: 702, 1940.
38. Hollander, L., and Vogel, H. R.: Acrosclerosis, Pennsylvania M. J. **43**: 1089, 1940.
39. Puddu, V.: Un caso de sclerodermia con calcificazioni, Policlinico (sez. prat.) **41**: 1801, 1934.
40. Weber, H.: Korresp. Bl. schwiz. Ärz. **8**: 623, 1878.
41. Hutchinson, J.: Acro-scleroderma following Raynaud's phenomena, Clin. J. **7**: 240, 1896.
42. Klemperer, P., Pollack, A. D., and Baehr, G.: Pathology of disseminated lupus erythematosis, Arch. Path. **32**: 569, 1941.
43. Klemperer, P., Pollack, A. D., and Baehr, G.: Diffuse collagen disease: acute disseminated lupus erythematosus and diffuse scleroderma, J. A. M. A. **119**: 331, 1942.
44. Weiss, Soma: Diseases associated with inflammatory lesions of the peripheral arteries, New England J. Med. **225**: 579, 1941.

45. Prinzmetal, M.: Mechanism of circulatory insufficiency in Raynaud's disease in association with sclerodactylia, Arch. Int. Med. **58**: 309, 1936.
46. Johnson, C. A.: A study of the clinical manifestations and the results of treatment of twenty-two patients with Raynaud's symptoms, Surg., Gynec. and Obst. **72**: 889, 1941.
47. Edwards, E. A., Hamilton, J. B., Duntley, S. Q., and Hubert, G.: Cutaneous vascular changes and pigmentary changes in castrate and eunuchoid men, Endocrinology **23**: 119, 1941.
48. Turner, H. H., Lackamn, E., and Hellbaum, A. A.: Effect of testosterone propionate on bone growth and skeletal maturation of normal and castrated male rats, Endocrinology **29**: 425, 1941.
49. Day, H. G., and Follis, R. H., Jr.: Skeletal changes in rats receiving estradiol benzoate as indicated by histological studies and determinations of bone ash, serum calcium, and phosphatase, Endocrinology **28**: 83, 1941.
50. Wentworth, J. H., Smith, P. K., and Gardner, W. V.: Composition of bones of mice receiving estrogens and androgens, Endocrinology **26**: 61, 1940.
51. Barlow, G. B.: Scleroderma associated with adrenal neoplasm, Arch. Dermat. and Syph. **39**: 1021, 1939.
52. Pacella, B. L., and Barrera, S. E.: Electroencephalography: its applications in neurology and psychiatry, Psychiatric Quart. **15**: 407, 1941.
53. Murphy, J. R., Krainin, P., and Gerson, M. J.: Scleroderma with pulmonary fibrosis, J. A. M. A. **116**: 499, 1941.
54. Linenthal, H., and Talkov, R.: Pulmonary fibrosis in Raynaud's disease, New England J. Med. **224**: 682, 1941.
55. Getzowa, S.: Cystic and compact pulmonary sclerosis in progressive scleroderma, Arch. Path. **40**: 99, 1945.
56. Baehr, G., and Pollack, A.: Diffuse vascular diseases, Mod. Concepts Cardiovas. Dis. **15**: (Dec.) 1946.
57. Pugh, D., Kvale, W. F., and Margulis, H.: Scleroderma with involvement of the viscera: report of a case, Proc. Staff Meet., Mayo Clin. **20**: 410, 1945.
58. Lindsay, J., Templeton, F., and Rothman, S.: Lesions of the esophagus in generalized progressive scleroderma, J. A. M. A. **123**: 745, 1943.
59. Jackman, J.: Roentgen features of scleroderma and acrosclerosis, Radiology **40**: 163, 1943.
60. Hale, C., and Schatzki, R.: The roentgenological appearance of the gastrointestinal tract in scleroderma, Am. J. Roentgenol. **11**: 407–420, 1944.
61. Guttmacher, A.: A case of severe scleroderma with successful delivery, Urol. and Cutan. Rev. **107**: 108, 1943.
62. Byron, C., and Michalover, S.: Calcinosis and scleroderma with parathyroidectomy, Ann. Int. Med. **18**: 2, 1943.
63. Rafsky, H., and Herzig, W.: Scleroderma with oesophageal symptoms, Gastroenterology **6**: 1, 1946.
64. Berchow, C., and Poppel, M.: Interstitial calcinosis circumscripta associated with scleroderma and Raynaud's disease, Radiology **39**: 96, 1942.
65. Olsen, A., O'Leary, P., and Kirklin, B.: Esophageal lesions associated with acrosclerosis and scleroderma, Arch. Int. Med. **76**: 189, 1945.
66. Goetz, R. H.: The pathology of progressive systemic sclerosis (generalized scleroderma), Clin. Proc. **4**: 337–392, 1945.
67. Graham, T. N.: Metabolic cutaneous calcinosis, Arch. Dermat. and Syph. **41**: 864, 1940.
68. Mathison, A. K., and Palmer, J. D.: Diffuse scleroderma with involvement of the heart; report of a case, Am. Heart J. **33**: 366, 1947.
69. Herstone, S., and Brower, J.: Werner syndrome, Am. J. Roentgenol. **51**: 639, 1944.
70. Bevans, M.: Pathology with special reference to changes in the G.I. tract, Am. J. Path. **21**: 25, 1945.

71. Leriche, R.: Sympathectomy for severe generalized scleroderma, complete case maintained for 7 years, Lyon chir. **37**: 79, 1941, 1942.
72. Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, D. T.: Scleroderma heart disease, Arch. Int. Med. **71**: 749, 1943.
73. Thomas, E. W. P.: Thibierge-Weissenbach syndrome, calcinosis cutis and scleroderma, Lancet **2**: 389, 1942.
74. Bauer, J.: Progressive facial hematrophy; disseminated scleroderma and muscular cramps, Confinia neurol. **7**: 3, 1946.
75. Lewin, G., and Heller, J.: Die Sclerodermie, 1895, A. Hirschwald, Berlin.
76. Thibierge, G., and Weissenbach, A.: Concretions calcaires sous-cutanées et sclérodermie, Ann. de dermat. et syph. **3**: 129, 1911.
77. Weber, F. P., and Scholefield, R. E.: Case of sclerodactylia with subcutaneous calcareous concretion, Brit. J. Dermat. **23**: 276, 1911.
78. Durham, R. H.: Scleroderma and calcinosis, Arch. Int. Med. **42**: 467, 1928.
79. Brody, J., and Bellin, D. E.: Calcinosis with scleroderma, Arch. Dermat. and Syph. **36**: 85, 1937.
80. Bauer, W., Marble, A., and Bennett, G. A.: Further studies in a case of calcification of subcutaneous tissue in a child, Am. J. M. Sc. **182**: 237, 1931.
81. Bolam, M.: Calcinosis with a report of a case of calcinosis universalis, Brit. J. Dermat. **47**: 340, 1935.
82. Wells, H. G.: Chemical pathology, 5th Ed., 1925, W. B. Saunders Co., Philadelphia, p. 493.
83. Norman, C. F.: Vitamin D therapy in the treatment of scleroderma and allied conditions; three cases, Geriatrics **2**: 24, 1943.
84. von Notthafft, A.: Neuere Arbeiten ueber Sklerodermie, Centralbl. f. allg. Path. u. path. Anat. **9**: 870, 1898.
85. Matsui, S.: Ueber die Pathologie and Pathogenese von Sklerodermie universalis, Mitt. a. d. med. Fak. d. k. Univ. zu Tokyo **31**: 55, 1924.
86. Kraus, E. J.: Zur Pathogenese der diffusen Skerodermie, Virchows Arch. f. path. Anat. **253**: 710, 1924.
87. Sellei, J.: Die Akrosklerosis Sklerodaktylie und deren Symptomenkomplex nebst neueren Untersuchungen bei Sklerodermie, Arch. f. Dermat. and Syph. **47**: 382, 1931.
88. Rake, G.: On the pathology and pathogenesis of scleroderma, Bull. Johns Hopkins Hosp. **48**: 212, 1931.
89. MacCallum, W. G.: Acute diffuse scleroderma, Tr. A. Am. Physicians **41**: 190, 1926.
90. Ehrman, S.: Ueber die Beziehung der Sklerodermie zu den autotoxischen Erythamen, Wien. med. Wchnschr. **53**: 1097, 1903.
91. Fessler, A., and Pohl, R.: Stenosierender Prozess des Oesophagus bei Sklerodermie, Dermat. Ztschr. **63**: 164, 1932.
92. Kure, K., Yamagata, L., Tsukada, S., and Hiyoshi, J.: Passagestörung des Oesophagus bei Sklerodermie und Dystrophia musculorum progressiva, Klin. Wchnschr. **51**: 477, 1936.
93. Goetz, R. H., and Rous, M. C.: Note on case showing Raynaud's phenomenon and additional manifestations, Clin. Proc. **1**: 244, 1942.
94. Dostrovsky, A.: Progressive scleroderma of the skin with cystic sclerodermal changes of the lungs, Arch. Dermat. and Syph. **55**: 1, 1947.
95. Podkaminsky, N. A.: Acroselerosis hyperplastica intraossa, Am. J. Roentgenol. **38**: 889, 1937.
96. Finlay, D. W.: Scleroderma, Middlesex Hosp. Rep. (1889) p. 29, cited by Luithelin f. *in* Mracek, F.: Handbuch der Hautkrankheiten, Vienna, A. Holder, **3**: 152, 1904.
97. Walker, S. A., and Benditt, E. P.: An electrophoretic study of the serum proteins in scleroderma, Proc. Soc. Exper. Biol. and Med. **67**: 504, 1948.
98. East, T., and Oram, S.: The heart in scleroderma, Brit. Heart J. **9**: 3, 1947.

99. Wuerthele-Caspe, V., Brodkin, E., and Mermod, C.: Etiology of scleroderma, J. M. Soc. New Jersey **44**: 256, 1947.
100. Jadassohn, J.: Arch. f. Dermat. u. Syph. **126**: 172, 1919, quoted by Cornbleet and Struck.[19]
101. Agatston, S. A., and Gartner, S.: Precocious cataracts and scleroderma, Arch. Ophth. **21**: 492, 1939.
102. Stafne, E. C., and Austin, L. T.: Characteristic dental findings in acrosclerosis and diffuse scleroderma, Am. J. Orthodontics (Oral Surg. Sect.) **30**: 25, 1944.
103. Rosenthal, I. H.: Generalized scleroderma hidebound disease its relation to the oral cavity with case history and dental restoration, Oral Surg., Oral Med. and Oral Path. **1**: 1019, 1948.
104. Duryee, A. W.: Scleroderma, Trans. Am. Ther. Soc. **42**: 127, 1942.
105. Leinwand, I.: Lipid and protein fractions. (3) Diseases of the mesenchyme, J. Lab. and Clin. Med. **37**: 532, 1951.
106. Kobat, E. A., Hangar, F. M., Moore, D. H., and Landow, H.: The relation of the cephalin flocculation and colloidal gold reactions to the serum proteins, J. Clin. Investigation **22**: 563, 1943.
107. Moore, H. C., and Sheehan, H. L.: The kidney of scleroderma, Lancet **1**: 68, 1952.
108. Evans, J. A., Rubitsky, H. J., and Perry, A. W.: Treatment of diffuse progressive scleroderma, J. A. M. A. **151**: 891, 1953.
109. Clinico-Pathologic Conference: Scleroderma with congestive heart failure, Am. J. Med. **14**: 231, 1953.

CASE REPORTS

HEREDITARY HEMORRHAGIC TELANGIECTASIA: A REPORT OF PULMONARY ARTERIOVENOUS FISTULAE IN MOTHER AND SON; MEDICAL (HORMONAL) AND SURGICAL THERAPY OF THIS DISEASE*

By EDWARD C. HEYDE, M.D., *Vancouver, Washington*

HEREDITARY hemorrhagic telangiectasia is one form of capillary heredopathia distinguished by the familial incidence of dilated small blood vessels histologically comprising a single layer of endothelium, with a conspicuous deficiency of muscular and elastic layers of the vessel walls.[1] The lesions are true vascular "spiders," such as one sees in pregnancy [2] and in acute or chronic liver disease. They occur most commonly on the oral and nasal mucosa, lips, face, arms and upper trunk, but may also be located in the viscera or, indeed, anywhere in the body. The association of pulmonary arteriovenous aneurysms (fistulae) with this disease has been emphasized by many articles in recent years.[3, 4, 5, 6, 7, 8] This paper reports a new family with the disease, the occurrence of pulmonary aneurysms in a mother and son of this family, and a probable pulmonary fistula with rupture and death in another member of the family. Hormonal therapy of the mucosal lesions causing epistaxis is also discussed briefly.

CASE REPORT

Case 1. I. B., male, age 45, has had frequent severe epistaxis ever since childhood. He has had pneumonia, pleurisy, influenza and scarlet fever. His general health has been good except for frequent attacks of bronchitis.

Examination on November 24, 1952, showed telangiectases on lips, tongue, nasal mucosa and face. The nasal septum was perforated from many cauterizations and a septal operation. The spleen was palpable two fingerbreadths below the left costal margin. There were no other significant physical abnormalities. He had a hypochromic anemia from recent severe epistaxes, but normal values for white cells, platelets, sedimentation rate, bleeding and coagulation times, total serum protein and A/G ratio, Bromsulphalein test and tourniquet test. The Kahn test was doubtful and the Eagle test positive, but negative in dilution. Chest fluoroscopy and films showed nothing suggestive of an aneurysm. Results of hormonal therapy will be discussed later in this paper.

Case 2. L. B., male, age six, is the son of I. B. This boy has one telangiectasis on his neck but no others. He does not have epistaxes, and his chest x-ray is normal.

Case 3. D. B., three and one half years old, is the other son of I. B. This child has epistaxes, especially with colds, and shows a few telangiectases on his nasal septum. His chest is normal on physical examination and x-ray.

Case 4. C. B. C., age 39, is the sister of I. B. She had repeated epistaxes for

*Received for publication December 28, 1953.

years until nasal radium therapy in 1940 gave her much benefit and practically stopped her nasal bleeding. Her bleeding was worst about age 18, and is aggravated now "around the time of menstruation" and when she becomes overheated. There is no history of hemoptysis.

Physical examination on February 14, 1953, showed telangiectases on the nasal mucosa, gums, lips, tongue and palate. There was a loud pulmonary bruit, maximal

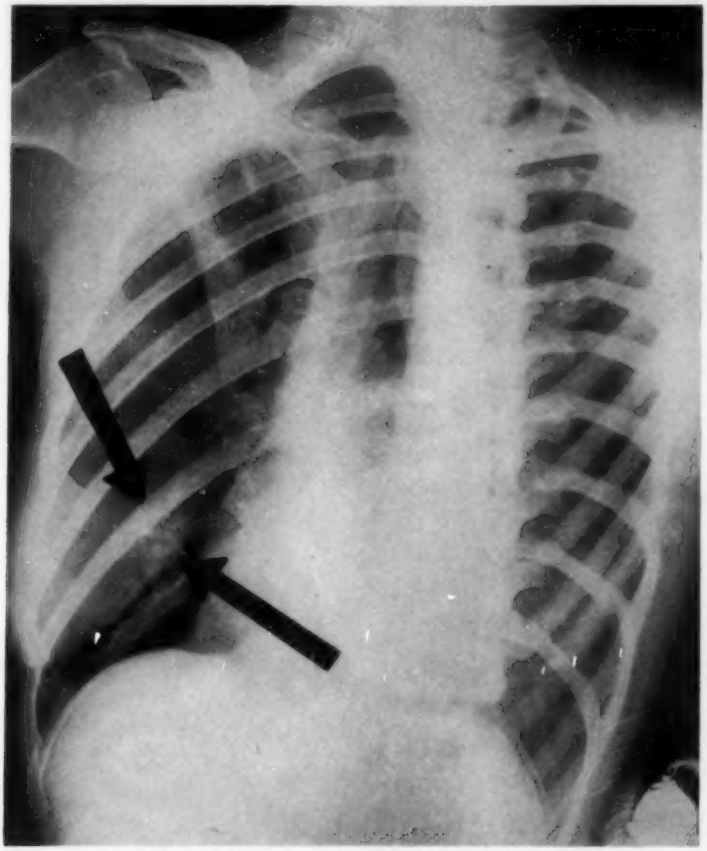


FIG. 1. Patient C. B. C., conventional LAO film.

over the anterior end of the right fifth rib. This murmur was to-and-fro, loud and roaring on deep inspiration and almost inaudible on forced expiration. It was about as loud as a grade 5 cardiac murmur. Fluoroscopy revealed a faint opacity about 3 cm. in diameter just within the chest wall under the area where the murmur was loudest. This shadow became larger on inspiration and was scarcely visible on expiration. There were no other significant physical abnormalities.

Laboratory Work: Hemoglobin, 13.8 gm.; red blood cells, 4.8 million; hema-

tocrit, 46 per cent; normal white cell count and differential count. Sedimentation rate, tourniquet test, bleeding and coagulation times were normal.

Conventional left anterior oblique (figure 1) and angiocardiographic x-rays (figures 2, 3) verified the physical and fluoroscopic diagnosis of a large pulmonary arteriovenous fistula in the right lower anterior chest. The angiocardiograms demonstrated two more (smaller) aneurysms in left upper lung and left lower lobe, the

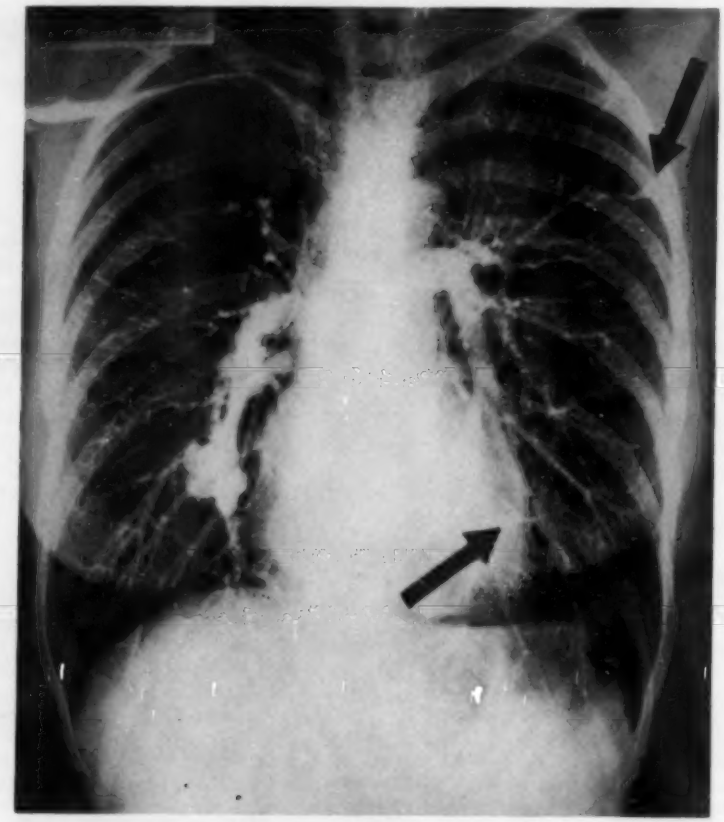


FIG. 2. Patient C. B. C., angiocardiogram.

latter, however, not seen on the lateral films. These are indicated by arrows in figure 2.

The large aneurysm was resected by Dr. William S. Conklin, of Portland, Oregon, on June 16, 1953. He was able by gentle dissection to isolate the aneurysm and remove it without any adherent lung tissue. The fistula was visible on the surface of the lung as a purplish 2 cm. bulge which could be deflated by occluding the tributary vessels with a ligature. The patient did very well postoperatively and went home in a week. She has some epistaxes now, but refuses estrogen therapy because of nausea.

Case 5. A. C., male, age 18, is the son of C. B. C. He has epistaxes "at odd times" but is otherwise healthy. He has no other abnormal bleeding.

Physical examination February 14, 1953, showed telangiectases on the nose, mouth, lips, tongue, sclera and palms. He has no other abnormalities on physical examination except acne. Laboratory work, including tourniquet test, hematocrit, bleeding and coagulation times, was all normal.

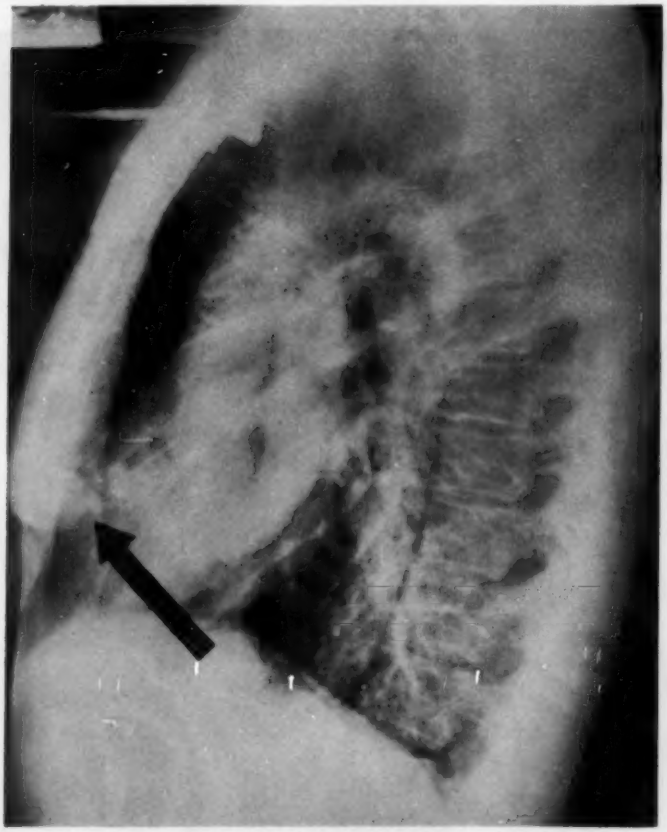


FIG. 3. Patient C. B. C., lateral angiocardiogram.

Conventional chest films showed a suspicious, small, sharply outlined density about 1 cm. in diameter far out in the left midlung field. Angiocardiograms showed that this was a small aneurysm (figure 4, arrow). I never heard a bruit in this area in spite of careful auscultation in all phases of respiration.

Case 6. W. B., male, age 53, brother of I. B. and C. B. C., had epistaxes "two or three hundred a year, sometimes two or three a day" until seven years ago. They were always worse at seeding time, when he treated his wheat with a chemical spray. His general health has always been good.

Examination showed many prominent telangiectases on face, nose, lips and nasal septum, some as large as a pinhead. The chest was normal, tourniquet test negative, and a chest x-ray showed no abnormalities. No laboratory work was done since he was examined at his ranch, far from any hospital facilities.

Case 7. Y. B. F., age 28, is the daughter of W. B. She has had epistaxes since childhood, worse just before menses, with no other abnormal bleeding. Epistaxis occurs about once a week and seems unrelated to anything except menstruation.

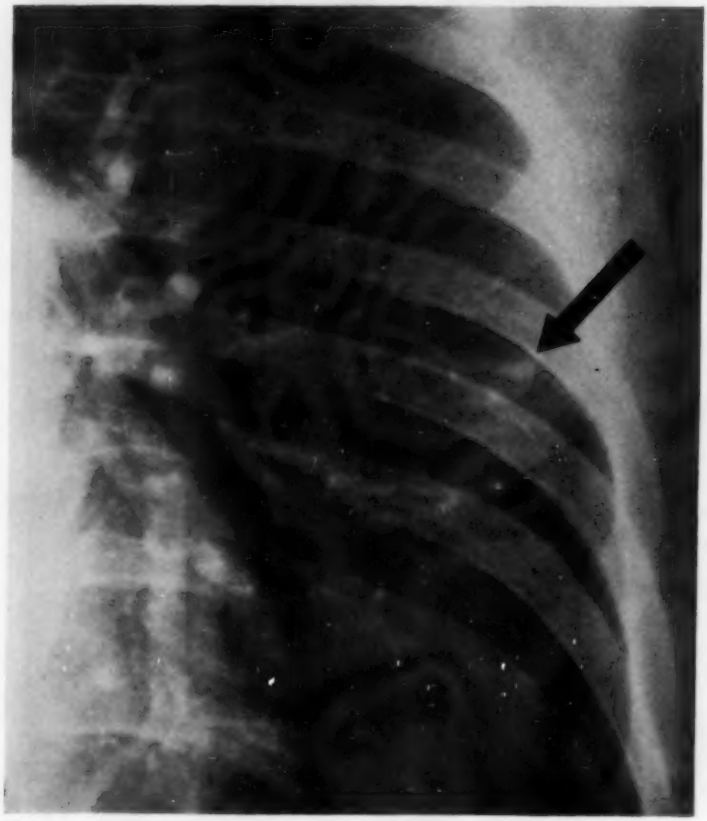


FIG. 4. Patient A. C., angiocardiogram.

Examination revealed telangiectases on forehead, lips, nasal septum and pharynx, with a few lesions in the V-area of the neck. The chest was normal on examination and x-ray.

Case 8. E. B. B., age 53 at her death in 1948, provided a most fascinating study in retrospect, since I never saw the patient. She had suffered from epistaxis all her life and had always been in poor health. Her brother, W. B., remembers that she was always pale and, in her later years, quite short of breath. In July, 1945, she com-

plained of intermittent left chest pain. In August, 1945, a chest x-ray showed multiple round masses in her left lower chest (figure 5). Bronchoscopy was done but nothing diagnostic was found and she returned to her home with a tentative diagnosis of pulmonary metastatic malignancies. At this time her blood count was 4.9 million red blood cells and the hemoglobin 15 gm., apparently in spite of her epistaxes.

On March 5, 1948, she had an attack of faintness and sudden pain in the left arm while sweeping. Her pulse was weak and thready and she was cyanotic when

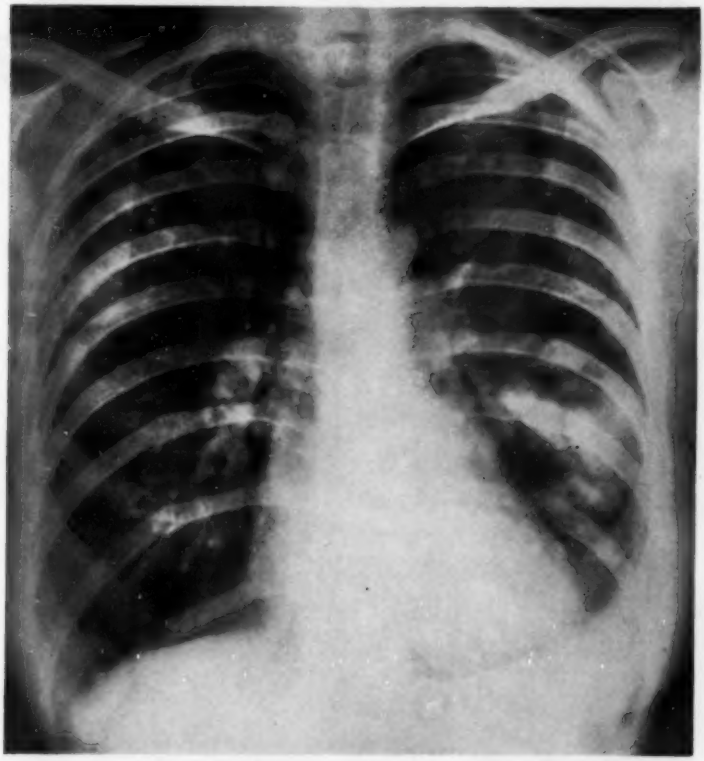


FIG. 5. Patient E. B. B., August, 1945.

examined in the hospital. She stayed two days and was discharged with a diagnosis of "? pulmonary tumors."

On October 4, 1948, she had just gone to bed when she told her daughter that she felt very weak and had pain in her left chest and arm. About a half-hour later the daughter was awakened by her mother's moans and found her struggling for air and with very severe left chest pain. At the hospital, her doctor found that the entire left chest was dull to percussion and that no breath sounds were audible on that side. Heart sounds were very weak and no pulse could be detected. She died one-half hour after admission. The final diagnosis was "atelectasis due to obstruction

of bronchi; malignant pulmonary metastases, primary site undetermined." No autopsy was done.

This patient's x-rays are shown in figures 5 to 8, inclusive. The appearance of the chest in August, 1945, and in March, 1948 (figures 5, 6 and 7) is about the same except for a slightly larger heart, more clouding of the left base, and perhaps a little increase in the size of the multiple round opacities. The lack of change in the densities seems to rule out the possibility that they were pulmonary neoplasms in 1945. The final film of October 4, 1948, shows massive obliteration of the left chest with a marked mediastinal shift to the right.

This patient's family and personal history, with this sequence of x-ray appearances, certainly suggests strongly that she had a large pulmonary arteriovenous fistula in the left lung, which bled once in March, 1948, and finally ruptured in October, 1948, causing her death from massive left hemothorax.

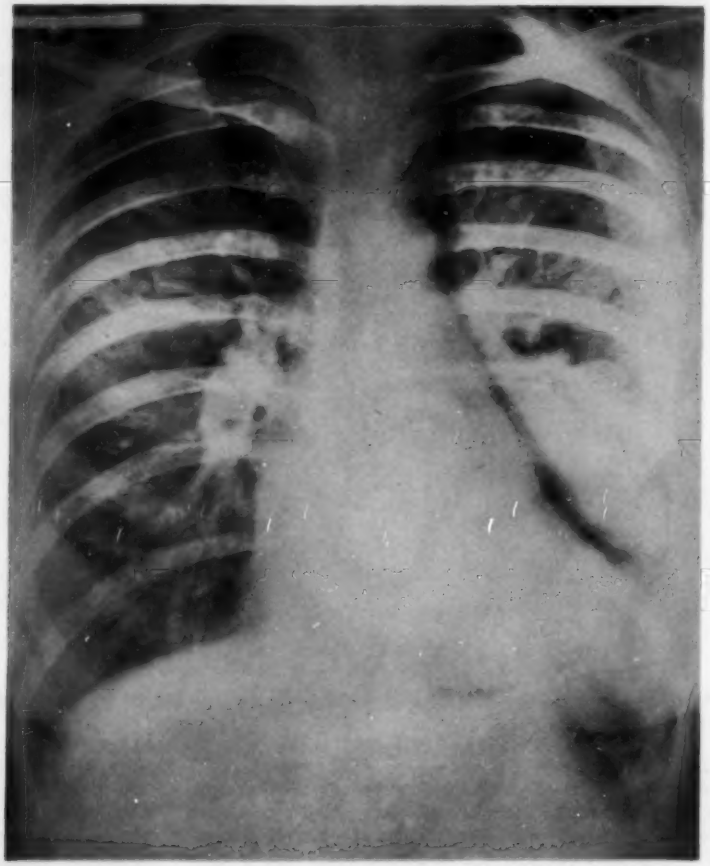


FIG. 6. Patient E. B. B., March 5, 1948.

FIG. 7. Patient E. B. B., March 5, 1948.

COMMENT

Of 36 members of this family whose histories are available, seven have the signs of hereditary hemorrhagic telangiectasia, and an additional four persons may have been affected. In most families with this disease it is clinically manifest in only one third of the members. If 11 out of a total of 36 persons reported here had clinical signs and symptoms, the proportion corresponds well to that usually given. It is obviously important for all the people in such a family to know about the disease, not only for proper therapy but also for the diagnosis of any pulmonary lesions which might appear on chest films and might easily be confused with tuberculoma, neoplasm and similar circumscribed masses in the lung. Twenty members of this family are young, several of them children, so the disease may become manifest in them around the age of puberty, when it often first appears. One of these patients (I. B.) has slight splenomegaly; the

others have no photosensitivity or hepatosplenomegaly, although both conditions have been reported in hereditary hemorrhagic telangiectasia.[5, 9] The tourniquet test is negative, as it is in this disease, although Singer and Wolfson [1] have reported a family with positive tests.

Pulmonary Arteriovenous Aneurysms

In this series there are one probable and two definitely proved cases of pulmonary fistulae of a total of 36 members of the family. I have found no statement in the literature giving the incidence of pulmonary A-V aneurysms in families having hereditary hemorrhagic telangiectasia. The proportion in my series does not give an accurate idea of the frequency of such lung abnormalities in this disease, since some of the people are dead (and could have had asymptomatic aneurysms), and some are children who may develop pulmonary aneurysms later.

Fig. 8. Patient E. B. B., October 4, 1948.

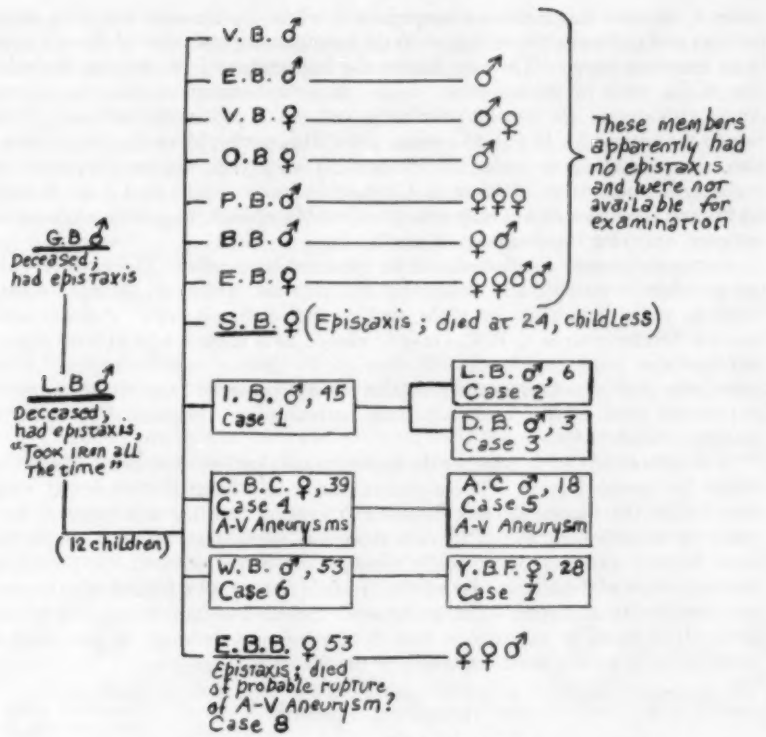

V. B. ♂
E. B. ♂ ——— ♂
V. B. ♀ ——— ♂♀
O. B ♀ ——— ♂
P. B. ♂ ——— ♀♀♀
B. B. ♂ ——— ♀♂
E. B. ♀ ——— ♀♀♂♂
These members apparently had no epistaxis and were not available for examination
G. B ♂
Deceased; had epistaxis
S. B. ♀ (Epistaxis; died at 24, childless)
L. B ♂
Deceased; had epistaxis, "Took iron all the time"
I. B. ♂, 45
Case 1
L. B. ♂, 6
Case 2
D. B. ♂, 3
Case 3
C. B. C. ♀, 39
Case 4
A-V Aneurysms
A. C ♂, 18
Case 5
A-V Aneurysm
(12 children)
W. B. ♂, 53
Case 6
Y. B. F. ♀, 28
Case 7
E. B. B. ♀ 53 ——— ♀♀♂
Epistaxis; died of probable rupture of A-V Aneurysm?
Case 8

FIG. 9. Family tree of the B—family.

The initials of members who probably had clinically apparent hereditary hemorrhagic telangiectasis are underlined; the initials of those examined and found to have the disease are boxed, with indications of sex and age.

In series of cases having pulmonary aneurysms, 50 per cent [5] to 60 per cent [6] of the patients also had cutaneous and/or mucosal telangiectases, so one should at least have a "high index of suspicion" for pulmonary fistulae on finding a patient with telangiectases and a family or personal history of epistaxis.

The lung lesions caused no symptoms in two of my patients (C. B. C. and A. C.), presumably because the fistulae were not large enough to produce a major arteriovenous shunt. When a large shunt does occur, the patient may have such symptoms as dyspnea, palpitation, dizziness, chest pain and headache, with physical findings of cyanosis, finger-clubbing and pulmonary murmurs, and with laboratory evidence of compensatory polycythemia. Patient E. B. B. (case 8) had dyspnea and cyanosis with chest pain in the attack seven months before she died.

Fluoroscopy is very helpful in identifying the pulmonary fistulae. If the patient is rotated slowly a mass may become visible which can be shown to be of vascular nature by using the Valsalva and Müller procedures. Patient C. B. C.

(case 4) showed this marked change in size when these maneuvers were used. Seaman and Goldman [8] have described the roentgenologic aspects of these lesions in an excellent paper. They emphasize the importance of recognizing the relation of the mass to the adjacent vessels, thus establishing its vascular nature. Angiocardiograms are usually conclusive and are a procedure with very little risk to the patient.[10] If a good routine chest film, preferably with oblique views also, shows nothing to make one suspect an aneurysm, angiocardiography is probably not necessary. Patient A. C. (case 5) had a small 1 by 1.5 cm. density on his routine chest film which was questionable enough to justify angiocardiography, verifying the diagnosis of aneurysm.

Large pulmonary fistulae should be removed surgically. The smaller ones can probably be watched and removed if they increase definitely in size, or if they begin to cause symptoms or signs such as polycythemia, etc. Patients with multiple fistulae such as C. B. C. (case 4) should have chest x-rays at least yearly, and perhaps angiocardiograms if the known lesions are enlarging. New aneurysms may develop; hence resection should conserve lung tissue as much as possible, since further operations may be necessary. Segmental resection is the best procedure.[6]

It is difficult to decide whether the asymptomatic patient with small aneurysms should be operated upon. These patients have two hazards threatening them even before the fistulae become large: (1) serious bleeding can come from a relatively small lesion, and (2) brain abscess is more likely in such people because bacteria can pass more easily through the fistula without the protective filtering action of the lungs. Israel and Gosfield [6] reported a patient who refused operation for an aneurysm 6 cm. in diameter and died of fatal hemoptysis a year later. It is probably not wise to wait until symptoms develop; surgery here is more properly prophylactic, especially if the fistula is large.

Hormonal Therapy

Recently Koch, Escher and Lewis [11] reported successful control of epistaxis in patients with hereditary hemorrhagic telangiectasia by giving estrogens to the female patients and estrogen-androgen tablets to the males. They based their treatment on the increased severity of epistaxes during periods of decreased estrogen secretion premenstrually and following x-ray castration. There is undoubtedly a connection between the sexual cycle, blood hormonal levels and the nasal mucosa: swelling and reddening of the nasal mucosa is a common finding in women during pregnancy, and degenerative changes in the nasal mucosa have been observed as a sequence to castration.[12] Estrogens cause a thicker, moister nasal mucosa and thus help protect the patient from epistaxis. They also have an apparently close relation to the formation of telangiectases. Bean et al.[2] found a direct correlation between increasing urinary estrogen excretion and the increasing numbers of telangiectases during pregnancy, with an abrupt drop in both factors following delivery. One might therefore expect epistaxis to increase when estrogens are given therapeutically, but apparently the protective action of thicker, moister nasal mucosa outweighs the increased telangiectasia formation. Two of my patients (C. B. C. and Y. B. F.) noted exacerbations of epistaxis premenstrually, and another (E. B. B.) "never had nosebleeds during menstruation." Patient W. B., although his telangiectases

are larger than those in any of the other persons examined, stopped having epistaxis at age 47. He has no symptoms suggesting male climacteric. Patients I. B. and W. B. said that their nasal bleeding was always worse when they had colds or when they worked in dry dusty environments, or with substances causing nasal irritation.

Only one patient in my series (I. B.) had epistaxes severe enough to make him willing to try estrogen-androgen therapy. He noted much improvement, especially in a reduction in the duration of individual bouts of epistaxis. Hormones did not prevent bleeding when he had upper respiratory infections; his nose had to be cauterized twice (even while taking hormones) when he "caught colds." He has taken no medication for three months now, and has maintained his improvement.

Summary

1. Seven members of a family of 36 have clinically obvious signs of hereditary hemorrhagic telangiectasia, and four additional members probably had the disease.

2. Of the 11 people who have (or probably had) the disease, two have proved pulmonary arteriovenous fistulae, while a third very likely had one which ruptured and caused her death.

3. Surgical resection is the best treatment for the pulmonary fistulae. Small lesions can probably be watched and operated upon if they become larger, but certain hazards remain even with the small fistulae.

4. Hormonal therapy seems to be helpful in controlling epistaxis in these patients and deserves a trial, at least when epistaxes are frequent and severe.

Acknowledgment

I wish to thank Dr. John Tuhy and Dr. Charles Dotter, of Portland, Oregon, and Dr. L. Allan Gay and Dr. Thomas E. Griffith, of The Dalles, Oregon, for their help in making this report possible.

BIBLIOGRAPHY

1. Singer, K., and Wolfson, W. Q.: Hemorrhagic telangiectasis; analysis of capillary heredopathies, New England J. Med. **230**: 637–642, 1944.
2. Bean, W. B., Cogswell, R., Dexter, M., and Embick, J. F.: Vascular changes of the skin in pregnancy: vascular spiders and palmar erythema, Surg., Gynec. and Obst. **88**: 739, 1949.
3. Symposium: Congenital familial hemorrhagic telangiectases (Clinical conference, Brooke General Hospital), Bull. U. S. Army M. Dept. **8**: 613–628 (Aug.) 1948.
4. Moyer, J. H., and Ackerman, A. J.: Hereditary hemorrhagic telangiectases associated with pulmonary arteriovenous fistula in two members of a family, Ann. Int. Med. **29**: 775–802 (Nov.) 1948.
5. Armentrout, H. L., and Underwood, F. J.: Familial hereditary hemorrhagic telangiectasia with associated pulmonary arteriovenous aneurysm, Am. J. Med. **7**: 246 (Feb.) 1950.
6. Israel, H. L., and Gosfield, E.: Fatal hemoptysis from pulmonary arteriovenous fistula: report of a case in a patient with hereditary hemorrhagic telangiectasia, J. A. M. A. **152**: 40 (May 2) 1953.
7. Tobin, J. R., and Wilder, T. C.: Pulmonary A-V fistula associated with hereditary hemorrhagic telangiectasia: report of occurrence in father and son, Ann. Int. Med. **38**: 868 (Apr.) 1953.

8. Seaman, W. B., and Goldman, A.: Roentgen aspects of pulmonary A-V fistula, Arch. Int. Med. **89**: 70, 1952.
9. Ashby, D. W.: Hereditary hemorrhagic telangiectasia with hepatosplenomegaly and ascites, Brit. M. J. **1**: 1059–1060 (May 12) 1951.
10. Dotter, C. T., and Jackson, F. S.: Death following angiocardiography, Radiology **54**: 527, 1950.
11. Koch, H. J., Escher, G. C., and Lewis, J. S.: Hormonal management of hereditary hemorrhagic telangiectasia, J. A. M. A. **149**: 1376–1380 (Aug. 9) 1952.
12. Best, C. H., and Taylor, N. B.: Physiologic basis of medical practice, 4th Ed., 1945, Williams & Wilkins Company, Baltimore.

HEREDITARY UNILATERAL HYDRONEPHROSIS *

By J. Floyd Cannon, M.D., *Salt Lake City, Utah*

The etiologic factors involved in cases of unilateral hydronephrosis are usually manifest from the results of a complete urologic study; however, there remains a group in which the etiology remains obscure. The two most common factors in the production of unilateral hydronephrosis, accounting for about 85 per cent of the cases, are calculi and ureteral constriction. Less common causes are stricture of the pelvis, ectopic kidney and aberrant vessels. Heredity has not previously been considered an etiologic factor. The hereditary factor present in the cases here reported indicates that this etiology should be considered when other causes are not discovered.

The family here presented had no knowledge of the presence of kidney disease until two infant boys demonstrated the disease in an advanced form, necessitating surgery. The family then sought advice as to the advisability of bearing subsequent children.

Figure 1 shows the family tree with the proved positive members indicated; all others are considered as normal. The size of the family and the number studied are too small to draw conclusions as to the hereditary pattern or type of transmission. It is noted, however, that all the positive members are males, and that in this small group only the males transmit the characteristic. The abnormality appears in three generations. No deaths have been known to have resulted.

Case Reports

Case 1. This seven week old infant (figure 1, Generation III, No. 4) was born at term after a 15 hour labor. The child, according to the mother, "almost died because a large abdomen complicated the delivery." At examination at birth, a flaring of the ribs was noted. There was a sagging of the flanks; however, no masses, tenderness, shifting dullness or fluid wave were noted.

The large abdomen was thought to be due to a megacolon. A colon x-ray study was done, with the following findings: "This colon appears quite normal on x-ray examination, except for displacement. There is no evidence of an intrinsic lesion of

* Received for publication January 29, 1954.

the colon. The entire colon and small intestine are displaced toward the left by a mass about 6 cm. in diameter which occupies the right side of the abdomen. The nature of this tumor cannot be determined from x-ray examination. Neither the liver nor kidney shadows are visible. The location of the mass is suggestive of kidney tumor." An x-ray study of the upper gastrointestinal tract was normal, except for the displacement described above. An intravenous pyelogram was done but neither kidney excreted sufficient dye to demonstrate the kidney configuration.

A right nephrectomy was performed. At operation a large, tense, hydronephrotic kidney was removed intact. The ureter was dilated to the limits of the incision, indicating the ureteral obstruction was at a low level.

The pathologic examination showed an oval cyst measuring 14 by 11 by 6 cm. Over one surface the cyst wall was thickened and beefy red, and grossly resembled kidney tissue. On section the cyst contained clear, straw-colored fluid and the cyst

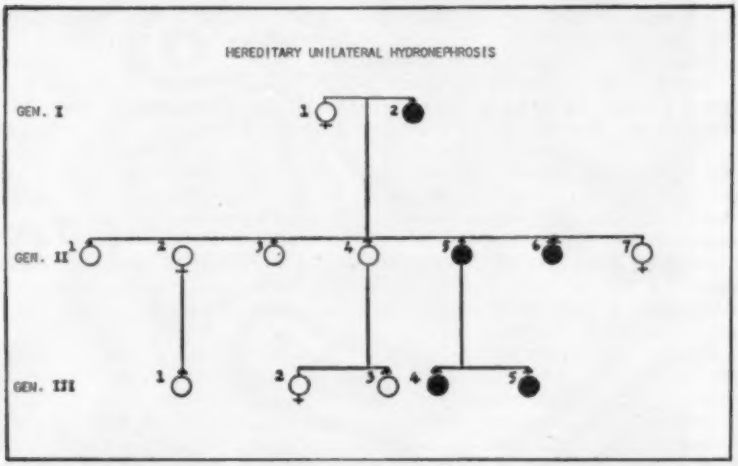


FIG. 1. Hereditary unilateral hydronephrosis in males of three generations.

lining was smooth and blue-gray in color, and contained numerous trabeculated diverticulum-like distortions. The cyst wall measured 0.8 cm. in its thickest portion and less than 0.1 cm. in other areas. There was no evidence of ulceration or tumor formation or demonstrable obstruction. Microscopic section showed kidney parenchyma with compressed tubules and glomeruli. The pelvic wall was a fibrous structure lined with transitional epithelium. The kidney capsule was intact.

The child made an uneventful recovery. Subsequently the child has had a right inguinal hernia, a hydrocele and a right undescended testicle repaired, and at three years of age is in good health.

Diagnosis: Congenital right hydronephrosis.

Case 2. This 11 month old child (figure 1, Generation III, No. 5) was first noted to have a mass in the abdomen at birth. On examination at 11 months, a firm protuberant mass was noted in the left upper quadrant. It was not movable and was apparently nontender.

In view of the findings in the older brother, an intravenous pyelogram was made.

No opaque material was excreted by the kidneys, so no information concerning the size and shape of kidney could be obtained.

At surgery a left nephrectomy was performed. The right kidney was palpated and found to be normal. The left kidney was exposed, revealing a large hydronephrosis, and the kidney was removed intact.

The pathologic examination showed a large cystic kidney which measured 13 by 8 by 4 cm. The renal surface and the renal pelvis comprised the walls of a large cyst, each comprising half of the total surface. A dilated segment of ureter was attached. The cyst contained straw-colored fluid. The renal substance measured only 3 mm. in thickness.

The microscopic sections revealed marked narrowing of the cortex and medulla. The kidney was congested and there were foci of lymphocytes in the cortex, largely at the periphery of the kidney tissue. Some scarring and depressions were present. The renal pelvis presented a moderate peripelvic reaction of lymphocytes. The ureter showed a mild lymphocytic reaction and the wall was thickened.

A pathologic diagnosis was made of hydronephrosis with mild pyelonephritis, nonspecific. The child recovered and at two years of age was in good health.

Diagnosis: Congenital left hydronephrosis.

Case 3. This 22 year old white male (figure 1, Generation II, No. 5), the father of cases 1 and 2, was a large, husky truck driver and was formerly a high school football player. He was entirely free of symptoms.

The urologic examination showed a normal urine. At cystoscopy the interior of the bladder was normal. Catheters passed readily to both kidneys. There was a good flow of normal urine from both sides. Cultures from the right and left kidneys showed no growth. Phenolsulfonphthalein, injected intravenously, appeared in five minutes from the right kidney and in seven minutes from the left kidney. During a 10 minute collection period, each kidney excreted 5 per cent of the dye (somewhat substandard, but the right catheter did not drip freely during the latter portion of the test and it is likely that renal function was better than indicated by these figures, especially on the right side).

Bilateral retrograde pyelograms were made. The right side of the urinary tract was normal. There was a rather large hydronephrosis on the left, and the 10-minute retention film showed great delay in the emptying time of the left kidney.

An intravenous urogram (figure 2) showed the pelvis of the left kidney to be unusually large. The major and minor calyces of the left kidney, however, were found to be within normal anatomic limits. The left ureter was relatively well visualized throughout its length. Nothing was seen to suggest the presence of obstruction in the left side of the upper urinary system. Evidently there was a congenitally large left renal pelvis. The opaque material remained in the renal pelvis for a period of at least two and one-half hours.

The right side of the upper urinary system and the urinary bladder were found to be normal.

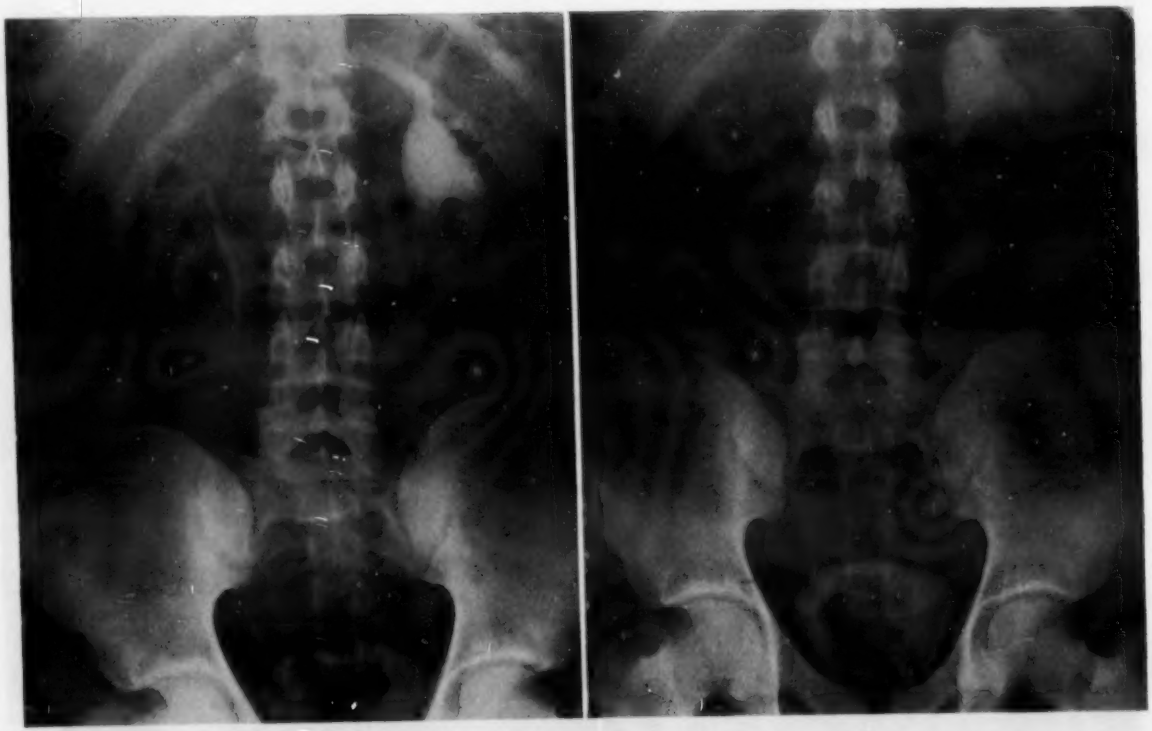
Diagnosis: Left congenital hydronephrosis.

Case 4. This 21 year old white female is the wife of case 3 (figure 1, Generation II, No. 5) and the mother of two children, cases 1 and 2. The patient had married at 18 years of age. The only significant event in her past history was a severe auto accident at 13 years of age, at which time she had had internal injuries.

An intravenous urogram showed the urinary system to be normal.

Case 5. This 17 year old white male laborer (figure 1, Generation II, No. 6) is the uncle of cases 1 and 2. He had no complaints and no symptoms of kidney disease. His past history was essentially negative, except for a hernioplasty one year prior to examination.

The patient was well developed, 69¼ inches in height and weighed 153 pounds. The blood pressure, pulse, temperature and physical findings were essentially normal.

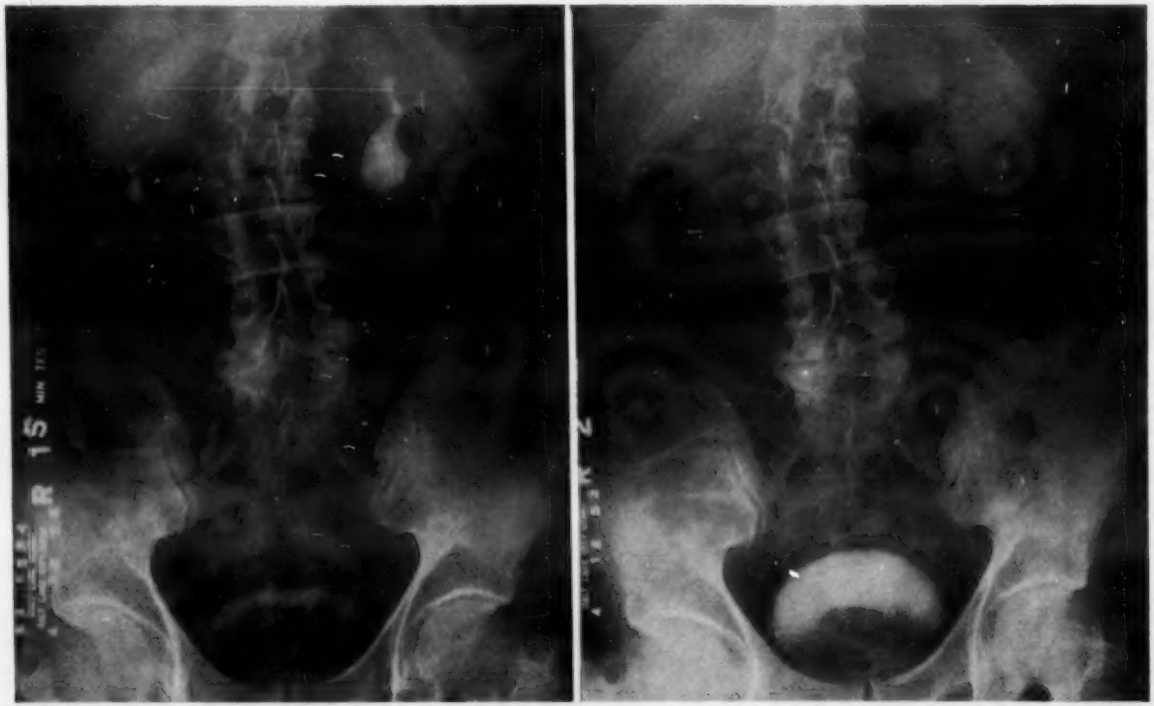


A B

FIG. 2. *Case 3.* *A.* Intravenous urogram, 30 minute post-injection. *B.* Intravenous urogram, one hour post-injection.

A B

FIG. 3. *Case 5. A.* Intravenous urogram, 30 minute post-injection. *B.* Intravenous urogram, one hour post-injection.



A *B*

FIG. 4. *Case 6. A.* Intravenous urogram, 15 minutes post-injection. *B.* Intravenous urogram, two hours post-injection.

The blood count and serologic test for syphilis were normal. The urine was found to be normal. On intravenous urography (figure 3), the left kidney emptied more slowly than the right and demonstrated a mild degree of hydronephrosis.

Diagnosis: Left congenital hydronephrosis.

Case 6. This 64 year old white male laborer (figure 1, Generation I, No. 1) is the grandfather of cases 1 and 2 and the father of cases 3 and 5.

The patient's history showed he had had diphtheria as a child and a tonsillectomy at 52 years of age.

The first symptoms of kidney disease were noted five years previous to the present study, at which time the patient noted a slow urinary stream with mild dysuria and occasional nocturia. He also complained of mild arthritis in both knees. At that time his urine was free from albumin and sugar. The sediment contained occasional pus cells and 4 to 8 red cells per high power field. His prostate was enlarged, Grade III benign. He had two ounces of residual urine. Cystoscopy showed a moderate degree of diffuse prostatic hypertrophy.

The present symptoms were discomfort in the left costovertebral area. His prostate was still enlarged and his voided urine showed 10 to 12 pus cells per high power field.

Cystoscopy revealed symmetric prostatic hypertrophy with an intravesical median lobe which made it difficult to visualize and catheterize his ureters. There were no stones, neoplasm or diverticula in the bladder.

Catheters were passed to both kidneys. Specimens from both sides showed numerous red cells (catheter trauma?) but no pus cells. Cultures from the right and left kidneys remained sterile. Phenolsulfonphthalein injected intravenously appeared in four minutes from the right kidney and in four and a half minutes from the left kidney. During a 10-minute collection period the right kidney excreted 10 per cent of the dye and the left kidney 5 per cent.

Intravenous pyelograms were made (figure 4). A definite left hydronephrosis was found present which on the absence of other etiology is assumed to be another example of a familial trait.

Diagnosis: Benign prostatic hypertrophy; hereditary unilateral hydronephrosis (left); diminished function of left kidney.

Summary

1. A family tree of unilateral hydronephrosis is presented.
2. The disease occurs in three consecutive generations.
3. Although the size of the family and the number studied are too small to draw conclusions as to the hereditary pattern or type of transmission, it is noted that all positive members are males and that the characteristic is transmitted through the males.
4. Heredity plays a part in the etiology of unilateral hydronephrosis.
5. The abnormality may be present at birth in a marked degree.
6. Symptoms and decrease in kidney function in the affected kidney are noted in the patient in advanced years.

Acknowledgment

The reference of cases 1 and 2 by Dr. Edward M. Jeppson and the urologic studies by Dr. R. P. Middleton are appreciated.

FALSE-POSITIVE REACTION TO THE REGITINE TEST FOR PHEOCHROMOCYTOMA: REPORT OF A CASE*

By RALPH D. ROSS, Commander, MC, U. S. Navy, *Corona, California*

REGITINE (preparation C-7337) or 2-{[N-(m-hydroxyphenyl)-p-toluidino] methyl}-2-imidazoline methanesulfonate lowers the blood pressure in patients with hypertension caused by a pheochromocytoma by blocking the pressor effect of epinephrine or norepinephrine in the blood.[1, 2] The drug exhibits adrenolytic as well as sympatholytic effects. Regitine effectively blocks the pressor substances for longer periods than does piperoxan, and in smaller amounts.[2] Therefore, regitine is considered more useful and less toxic than piperoxan as a diagnostic agent to exclude the presence of pheochromocytoma as the cause of paroxysmal or sustained hypertension.[2] In many hospitals and clinics the regitine test has replaced the piperoxan test as a routine procedure. The benzodioxane test should be employed as a confirmatory test when the results of the regitine test are in doubt.

The histamine test is considered to be most accurate in the diagnosis of pheochromocytoma that causes paroxysmal hypertension, whereas regitine produces the most reliable results when a sustained hypertension exists.[3]

Grimson et al.[4] reported regitine to be effective in controlling the blood pressure in a patient with pheochromocytoma before and during surgery. During recent years many authors have reported the use of regitine as a valuable diagnostic or therapeutic drug.[1-20] Many of these authors have reported false-positive reactions to the regitine diagnostic test for pheochromocytoma. Various drugs, such as sedatives, narcotics and other blood pressure lowering agents, influence the blood pressure during the pharmacologic tests for pheochromocytoma and may give false-positive results. False-positive reactions to the regitine test have commonly been seen in patients with uremia.

The patient herein reported had a positive reaction to the regitine test and had been on no sedatives, narcotics or other medication and was not found to be in uremia. A careful and complete postmortem examination revealed no pheochromocytoma.

CASE REPORT

A 35 year old Hawaiian housewife was admitted to the hospital on September 25, 1953. She had been asymptomatic until approximately one hour before admission, at which time a severe headache developed. This was associated with profuse perspiration and marked generalized weakness, and was followed within a few minutes by coma. She developed considerable respiratory distress and a tachycardia at that time.

The patient had been under observation by her family physician for hypertension for the last several years. She had been told that her blood pressure had been normal on many occasions, whereas at other times it was markedly elevated. Paroxysmal symptoms of nausea, vomiting, headache and profuse perspiration had developed at variable intervals. Her blood pressure during these symptoms had been found to be elevated on numerous occasions. She had recently been on no medication of any type.

* Received for publication January 15, 1954.

There was no known past history of renal disease. The past and family histories were otherwise not contributory to the present illness.

The physical examination at the time of her admission to the hospital revealed a comatose, moderately obese female who did not respond to stimulation. The blood pressure was 300/180 mm. of Hg and the apical rate was 170 per minute. The respirations were labored and the respiratory rate was 40 per minute. The right pupil was larger than the left and there was lateral deviation of the right eye. A funduscopic examination showed evidence of early papilledema and changes consistent with a grade one Keith-Wagener retinopathy. A paresis of the right facial muscles and a flaccid paralysis of all extremities were noted. The deep tendon

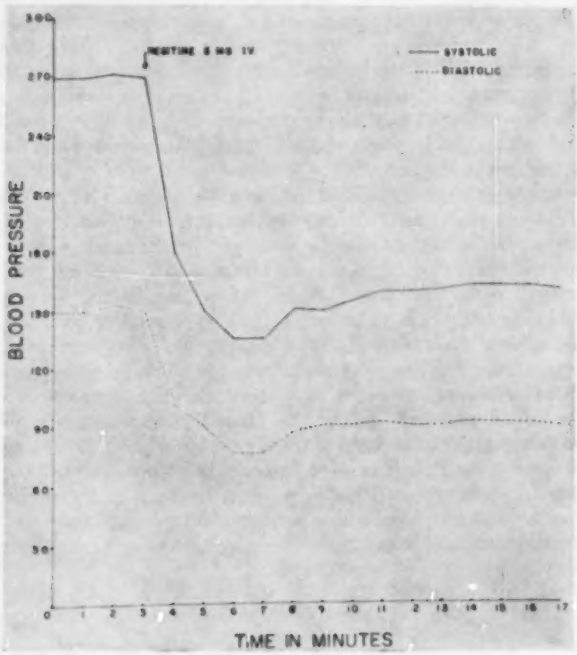


FIG. 1. Regitine test, C. E. B.

reflexes were present on the right and absent on the left. No pathologic reflexes were elicited. The examination was otherwise not remarkable.

An electrocardiogram showed a supraventricular tachycardia at a rate of 180 per minute and evidence of left ventricular hypertrophy. A nonprotein nitrogen was 30.5 mg. per 100 ml. and a blood glucose was 208 mg. per 100 ml. A urinalysis revealed a 2 plus albuminuria and a specific gravity of 1.015.

A regitine test, using 5 mg. intravenously, showed a drop in the blood pressure from a baseline level of 270/150 to 140/80 mm. of Hg in a period of three minutes (figure 1). A repeat regitine test similarly reduced the blood pressure from a baseline level of 300/160 mm. of Hg.

At the time of admission a 500 ml. phlebotomy was performed, and a full

digitalizing dosage of lanatoside C (Cedilanid) intravenously, continuous oxygen, aminophylline and regitine were given. The blood pressure was well controlled by the administration of regitine. A ventricular tachycardia occurred (figure 2), and quinidine gluconate was given intravenously. In spite of this a ventricular fibrillation developed (figure 2), and the patient died less than six hours after the onset of symptoms.

A postmortem examination revealed a massive cerebral hemorrhage on the right, advanced arteriolar nephrosclerosis (figure 3), cardiac hypertrophy (1,050

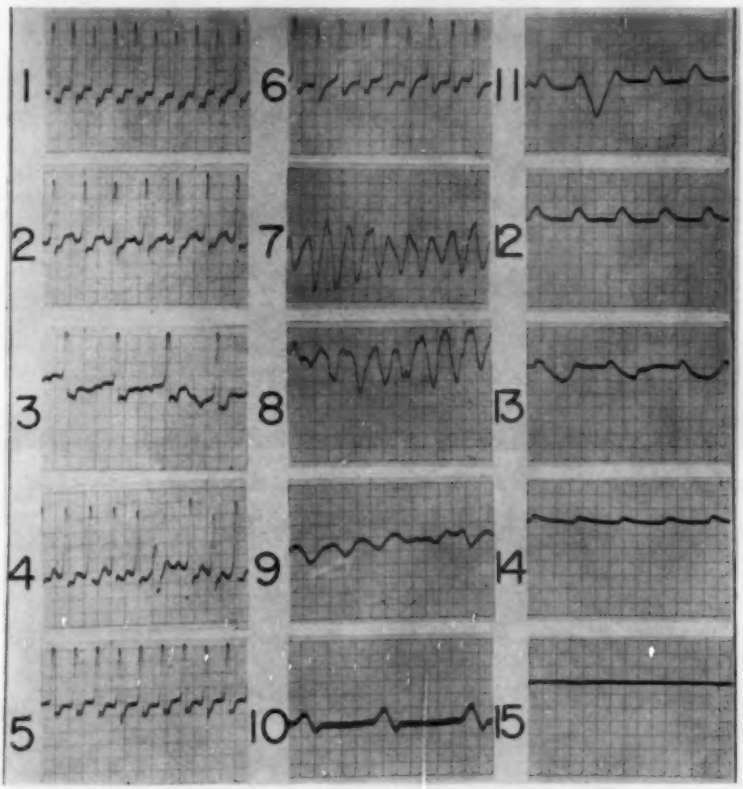


FIG. 2. Electrocardiographic tracings in Lead II, showing various arrhythmias.

gm.) (figure 4), and cerebral arteriosclerosis. A thorough and complete search was made for a chromaffin tissue tumor in all possible locations but none was found.

SUMMARY AND CONCLUSIONS

A case is presented of a patient with a history of paroxysmal hypertension demonstrating a false-positive reaction to the regitine test. She had received no medication prior to the test. The nonprotein nitrogen was 30.5 mg. per 100

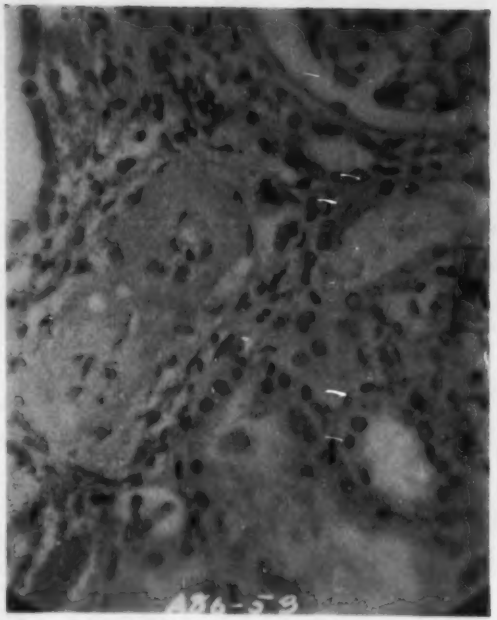


FIG. 3. Photomicrograph of kidney, showing nephrosclerosis.

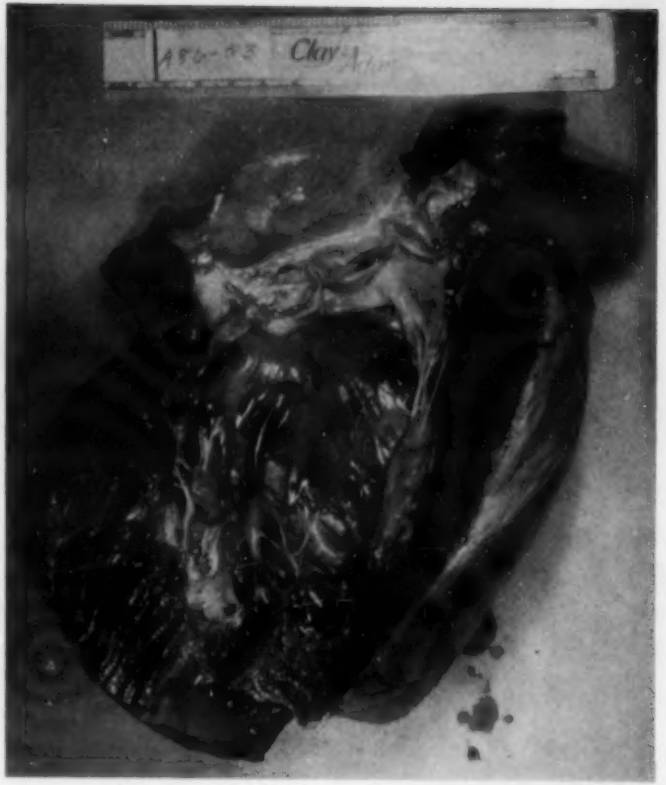


FIG. 4. Photograph of heart, showing left ventricular hypertrophy.

ml. The basal blood pressures were in a definitely hypertensive range before the test. A confirmatory benzodioxane test was not performed in this case.

BIBLIOGRAPHY

1. Roth, G. M., Dockerty, M. B., and Hightower, N. C., Jr.: Pheochromocytoma from the laboratory standpoint, S. Clin. North America **32**: 1065–1077 (Aug.) 1952.
2. Council on Pharmacy and Chemistry, Phentolamine hydrochloride, J. A. M. A. **152**: 1533–1535 (Aug. 15) 1953.
3. ReMine, W. H., Estes, J. E., Jr., Dockerty, M. B., and Priestley, J. T.: Hemiplegia resulting from pheochromocytoma, report of case, J. A. M. A. **152**: 808–811 (June 27) 1953.
4. Grimson, K. S., Longino, F. H., Kernodle, C. E., and O'Rear, H. B.: Treatment of a patient with a pheochromocytoma, use of an adrenolytic drug before and during operation, J. A. M. A. **140**: 1273–1274 (Aug. 20) 1949.
5. Anderson, W. H., Rolufs, L. S., and Doerner, A. A.: The use of pharmacological tests in the diagnosis of pheochromocytoma, Am. Heart J. **43**: 252–263, 1952.
6. Gifford, R. W., Jr., Roth, G. M., and Kvale, W. F.: Evaluation of new adrenolytic drug (regitine) as test for pheochromocytoma, J. A. M. A. **149**: 1628–1634 (Aug. 30) 1952.
7. Calkins, E., Dana, G. W., and Howard, J. E.: Current methods of diagnosis of pheochromocytoma, J. A. M. A. **145**: 880–884 (Mar. 24) 1951.
8. Emlet, J. R., Grimson, K. S., Bell, D. M., and Orgain, E. S.: Use of piperoxan and regitine as routine tests in patients with hypertension, J. A. M. A. **146**: 1383–1386 (Aug. 11) 1951.
9. Lyons, R. H., and Love, V. L.: Clinical aspects of ganglionic and adrenergic blocking agents, *in* Dock, W., and Snapper, I.: Advances in internal medicine, Vol. V, 1952, The Yearbook Publishers, Chicago, pp. 303–336.
10. Corr, W. P.: The management of high blood pressure, M. Clin. North America **36**: 1013–1024 (July) 1952.
11. Bannon, W. G., and Allen, E. V.: The effect of adrenolytic drugs on pheochromocytoma with functioning metastatic lesions: report of case, Proc. Staff Meet., Mayo Clin. **27**: 459–464 (Nov. 5) 1952.
12. Gifford, R. W., Jr., Roth, G. M., and Kvale, W. F.: The evaluation of use of regitine (C-7337) as a new pharmacologic test for pheochromocytoma, J. Lab. and Clin. Med. **38**: 812 (Nov.) 1951.
13. Grimson, K. S., Emlet, J. R., and Hamblen, E. C.: Diagnosis and management of tumors of the adrenal gland, Ann. Surg. **134**: 451–463 (Sept.) 1951.
14. Iseri, L. T., Henderson, H. W., and Derr, J. W.: Use of adrenolytic drug, regitine, in pheochromocytoma, Am. Heart J. **42**: 129–136 (July) 1951.
15. Longino, F. H., Grimson, K. S., Chittum, J. R., and Metcalf, B. H.: Effects of a new quaternary amine and a new imidazoline derivative on the autonomic nervous system, Surgery **26**: 421–434 (Sept.) 1949.
16. Console, A. D., Dunbar, H. S., and Ray, B. S.: Pheochromocytoma, the use of adrenergic blocking agents in the operative management, Surgery **28**: 428–437 (Aug.) 1950.
17. Moyer, J. H., and Caplovitz, C.: The clinical results of oral and parenteral administration of 2-(N'p-tolyl-N'm-hydroxyphenylaminomethyl) imidazoline hydrochloride (regitine) in the treatment of hypertension and an evaluation of the cerebral hemodynamic effects, Am. Heart J. **45**: 602–610 (Apr.) 1953.

18. Sprague, R. G., Kvale, W. F., and Priestley, J. T.: Management of certain hyperfunction lesions of the adrenal cortex and medulla, J. A. M. A. **151**: 629–639 (Feb. 21) 1953.

19. Clarke, C. W., Jr., Hays, D. R., Jr., Van Itallie, T. B., and Thompson, I. M.: Clinical appraisal of a new adrenergic blocking agent: effect of regitine on digital blood flow in normal subjects and patients with peripheral arterial disease, Circulation **8**: 715–722 (Nov.) 1953.

20. Ross, R. D., Mitchell, R. E., Larsen, W. E., and Dillon, J. R.: Pheochromocytoma: report of two cases successfully treated by surgical removal, to be published.

WHIPPLE'S DISEASE (INTESTINAL LIPODYSTROPHY): REVIEW OF THE LITERATURE AND REPORT OF A CASE SUCCESSFULLY TREATED WITH ADRENOCORTICOTROPIN (ACTH) AND CORTISONE*

By JEROME RADDING, M.D., and MARSHALL J. FIESE, M.D., *Fresno, California*

IN 1907 Whipple [1] reported a previously undescribed disease which occurred in a 36 year old physician and was manifested by vague abdominal distress, progressive weight loss, diarrhea, arthralgia and generalized pigmentation. Stool examination showed a great increase in neutral fat and fatty acids. The patient died following an exploratory laparotomy, and microscopic examination revealed an accumulation of mononuclear foam cells in the lamina propria of the small intestine and in the enlarged mesenteric lymph nodes. Whipple named the disease intestinal lipodystrophy, and felt that it was due to some disorder of fat metabolism.

Since Whipple's description of this disease 52 acceptable cases have been reported.[2, 3, 4, 6, 7, 8, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, 34, 36, 37, 38, 39, 40, 41, 42, 43, 46, 47, 48, 49, 50, 51, 52, 53, 54] There have been extensive reviews of the subject by Hendrix and his co-workers,[26] Plummer and his co-workers,[38, 54] and by Russo.[49] Most authors consider the three cases of Blumgart,[2] the three cases of Pemberton,[25] Frei's first case, [7] and sirgle cases reported by Collins,[5] Boeck [8] and Pearse [14] as unacceptable either because they did not fit the clinical picture, or represented chylous obstruction, or because the diagnosis was not confirmed by adequate biopsy or postmortem studies. To these unacceptable cases can be added that reported by Inguscio,[44] inasmuch as it lacked pathologic proof and the clinical response of the patient to vitamins and "anti-anemic" preparations suggested sprue.

Forty-four of the 53 previously reported cases have succumbed to the disease despite many therapeutic measures, which have included various diets, all of the vitamins, blood transfusions, liver extract, parenteral protein hydrolysates, oral

* Received for publication March 5, 1954.
From the Medical Service, Veterans Administration Hospital, Fresno.

polysorbates, aqueous adrenal cortical extract, desoxycorticosterone acetate, and even roentgen therapy. Of the remaining nine cases,[24, 33 (case 3), 41, 42, 46, 47, 48, 52, 54] four [24, 33 (case 3), 41, 42] were alive at the time of publication of the case report, but no further information could be found on the final outcome of the disease. Luton's patient [46] was reported to be improved after treatment for hypopotassemia, and Paulley's patient [48] was improved after receiving psychotherapy for an "intestinal constitution" and two courses of chloramphenicol to control secondary infection. Mendes De Leon,[47] Jones and others,[52] and Plummer and others [54] report remarkable remissions of the disease after treatment with adrenocorticotropic hormone or cortisone. Mendes De Leon's patient received only adrenocorticotropic hormone, Jones's patient received adrenocorticotropic hormone followed by cortisone, and Plummer's patient responded to administration of adrenocorticotropic hormone after being found refractory to cortisone. Wallace's patient [51] received adrenocorticotropic hormone for one week prior to death, but the diagnosis was not established until postmortem examination was done. The patient of Story and Sagild [53] did not respond to cortisone and died after four weeks of therapy. Janowitz' patient [45] responded well on successive occasions to cortisone, adrenocorticotropic hormone and hydrocortisone, but the results have not been published yet, so that his case is not included in this study.

A report of the fifty-fourth published case of Whipple's disease follows, this being the fourth in which the patient has shown a dramatic response to administration of adrenocorticotropic hormone and cortisone.

Case Report

History: A 62 year old white married male truck driver entered the Fresno Veterans Administration Hospital on April 1, 1953, complaining of diarrhea and weight loss. For many years he had noted a migratory arthralgia in the lumbar spine and various peripheral joints without any evidence of swelling of the joints. For six years he had experienced attacks of knifelike lower abdominal pain associated with abdominal distention. Between 1947 and 1952 there was a gradual 20 pound (9 Kg.) weight loss, and during the next year an additional 20 pounds (9 Kg.) had been lost, so that he weighed 107 pounds (48 Kg.) at the time of admission. During the year prior to admission to the hospital there was a diarrhea with passage of from two to five foamy, watery, foul-smelling stools every day. There had been anorexia for four months, and a chronic nonproductive cough for many years.

Physical Examination: The patient was an emaciated white male whose skin had a faint grayish yellow discoloration. His weight was 107 pounds (48 Kg.). The blood pressure was 110 mm. of Hg systolic and 60 mm. diastolic. The temperature was 98° F. (36.6° C.), the pulse rate was 84 per minute, and the respiratory rate, 16 per minute. The tongue was smooth but pink. The heart and lungs were normal. A sharp, smooth, nontender liver edge was palpable at the right costal margin. There was a long, healed right lower quadrant abdominal scar from a previous appendectomy. There was slight tenderness in the periumbilical area and also in the right lower quadrant. No abdominal masses were palpable. Digital rectal examination and sigmoidoscopic visualization were entirely normal. One firm, very slightly enlarged lymph node was palpated in each axilla. There was no evidence of swelling, increased temperature or deformity of any of the joints.

Laboratory Studies: The red blood cell count was 4.04 million per cubic millimeter, the hemoglobin was 9.8 gm. per 100 c.c., the hematocrit reading was 34 vol.

per cent, and the sedimentation rate was 54 mm. in one hour. The white blood cells numbered 13,800 per cubic millimeter, with 84 per cent segmented neutrophils, 7 per cent unsegmented neutrophils, 7 per cent lymphocytes and 2 per cent eosinophils. The urine had a specific gravity of 1.025 and a trace of albumin, and showed a negative microscopic examination. Total serum protein was 5.4 gm. per 100 c.c., with an albumin of 3.2 gm. per 100 c.c., and a globulin of 2.2 gm. per 100 c.c. The serologic test for syphilis was negative. Examination of the stool revealed no ova or parasites, and a stool culture revealed no pathogenic organisms. Total serum cholesterol was 143 mg. per 100 c.c. Basal metabolic rate determinations were plus 65 and plus 54, but the protein bound blood iodine was 3.6 micrograms per 100 c.c. A glucose tolerance curve was normal. Serum sodium was 147 mEq. per liter, and the serum potassium, 5.4 mEq. per liter. A total eosinophil count was 663 per cubic millimeter before, and 337 per cubic millimeter four hours after injection of 25 mg. of adrenocorticotropic hormone. An initial 24 hour stool examination showed a total weight of 950 gm., 40.2 per cent of the dry weight consisting of fat. The roentgenogram of the chest was normal. The roentgenogram of the colon after a barium enema was normal. Roentgenograms of the gastrointestinal tract showed coarsening of the small intestinal mucosa, interpreted as representing a nutritional disturbance.

Course in Hospital: The patient was first treated symptomatically for the diarrhea and was given four 500 c.c. blood transfusions for control of the anemia. He was afebrile during his hospital course. Large doses of all of the vitamins were administered and he was given a low-residue diet, without any effect on the diarrhea or steatorrhea. He was then given a high protein, high carbohydrate, low fat diet, with oral pancreatin and Sorlate, without any effect on his symptoms. On June 3, 1953, a right axillary lymph node was excised and the microscopic picture was that of a nonspecific chronic lymphadenitis.

On June 16 an exploratory laparotomy was performed because the patient continued a progressive downhill course. The differential diagnosis prior to laparotomy included regional enteritis, partial obstruction of the small intestine due to adhesions, and Whipple's disease. The wall of most of the small intestine appeared to be thickened, and minute accumulations of yellow, fatty-appearing material could be seen under the serosa. Multiple large, discrete yellow lymph nodes were noted in the region of the superior mesenteric artery, two of which were removed for microscopic examination, revealing a picture typical of Whipple's disease. The lymph follicles were absent and the nodes contained many large vacuoles. The intervening stroma was infiltrated with many mononuclear cells with foamy cytoplasm (figure 1). These mononuclear foam cells gave a positive reaction for glycoprotein with the periodic-acid-Schiff technic (figure 2).

On June 23, 1953, administration of adrenocorticotropic hormone was begun. The patient received 20 mg. intramuscularly every six hours for the first week, 15 mg. every six hours for the second week, and 10 mg. every six hours for the following two days. Then he was given oral cortisone in doses of 200 mg. the first day, 100 mg. daily for a period of two weeks, and rapidly decreasing amounts for two more days. The total course of steroid therapy lasted one month. Within 24 hours after treatment was started his diarrhea ceased, and from then on he had one formed stool each day. The total 24 hour fecal weight decreased from 950 gm. to 72.5 gm. in eight weeks, and the fat content of the dried stool decreased from 40.2 per cent to 30.5 per cent. There was a weight gain of 30 pounds (14 Kg.) during the same period.

Six months after the course of adrenocorticotropin and cortisone therapy the patient still continued to have one normal appearing formed stool each day and had

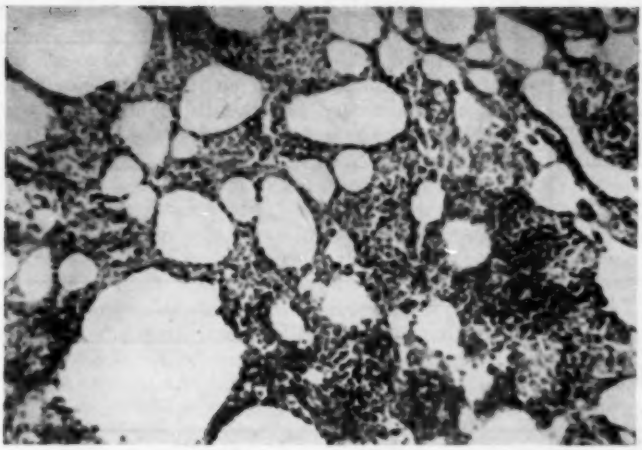


FIG. 1. Photomicrograph of section of mesenteric lymph node, illustrating absence of lymph follicles and presence of large vacuoles (H & E stain × 80).

maintained his weight at 134 pounds (61 Kg.). His blood pressure was 150 mm. of Hg systolic and 80 mm. diastolic. However, he continued to experience migratory arthralgia, the white cell count was 15,700 per cubic millimeter, and the sedimentation rate was 45 mm. in one hour, indicating that the disease process was not cured but was merely in a state of symptomatic remission (figure 3).

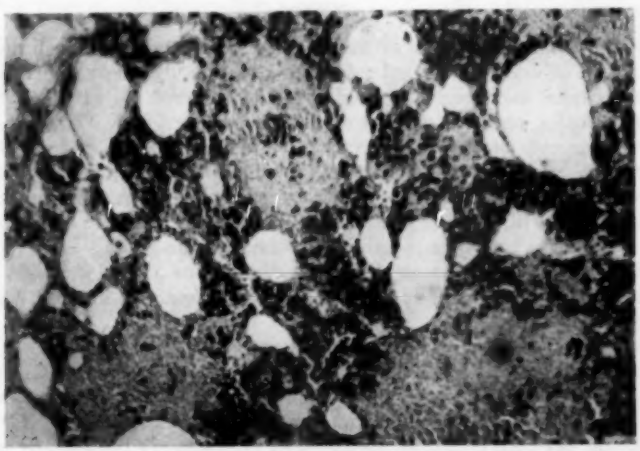


FIG. 2. Photomicrograph of section of mesenteric lymph node, illustrating deeply stained mononuclear foam cells (periodic-acid-Schiff stain × 80).

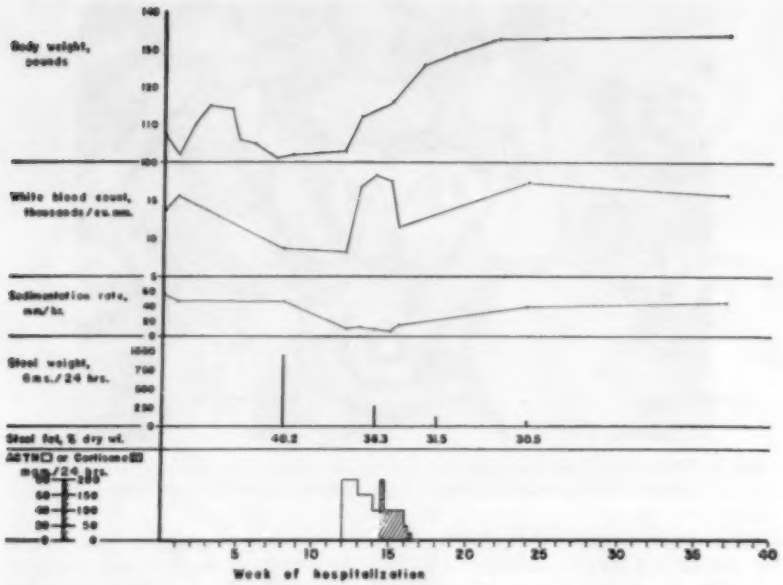


FIG. 3. Clinical course of a patient with Whipple's disease treated with adrenocorticotropin (ACTH) and cortisone.

COMMENT

Clinical Picture: A review of the 54 reported cases shows that the usual history is that of vague abdominal pain and distention, diarrhea, arthralgia, progressive weakness and weight loss (table 1). All except five of the cases have occurred in males, and although the age range has been from 17 months to 74 years, the majority of the cases occur between the ages of 30 and 60. The duration of the disease from the onset of symptoms has ranged from five months to 36 years, with the average being slightly over five years. Weight loss occurred in all but one patient, varying from 15 to 102 pounds. In those cases in which the specific findings have been mentioned, abdominal pain and distention occurred in all of 47 patients, diarrhea in all of 51, arthralgia in 36 of 44, weight loss in 50 of 51, and cough in all of 14. Arthralgia usually preceded the diarrhea, often by many years.

Physical examination ordinarily reveals varying degrees of weight loss and emaciation, and the patient exhibits hypotension (40 of 43), abdominal distention (all of 47), a doughy abdomen or palpable abdominal mass (25 patients), and a peculiar gray or brown pigmentation of the skin (all of 30 patients). The pigmentation has been compared to that seen in Addison's disease and has also been described as "muddy" in appearance. Fitzgerald and Kinney's patient [21] was jaundiced, but also had splenomegaly, leukocytosis, increased fragility of the red blood cells and a hemolytic anemia. No other patients were reported

as being jaundiced. The spleen was palpably enlarged in three patients and the liver in three other patients.

Forty-five of 46 patients had an anemia which was described as "secondary" or hypochromic. No mention was made of the blood counts in eight other patients. Twenty-three patients had gastric analyses, and achlorhydria was found in 17. Serum proteins were decreased in 13 of 23 patients. Of 24 patients whose stools were examined for fat content, 20 exhibited increased fat ranging from 34 per cent to 60 per cent of the dried weight of the stool. Nineteen patients had glucose tolerance studies, revealing a low or flat curve in 13, a normal curve in four, and a diabetic curve in two. Roentgenograms of the gastrointestinal tract were done in 28 patients, and 24 showed either hypomotility or irritability of the small intestine, or segmentation and puddling of the barium in the small intestine, interpreted as representing a deficiency pattern.

The wall of the small intestine is thickened and the serosa often contains minute yellow flecks. The mesenteric and retroperitoneal lymph nodes are enlarged, yellow or gray, and have a cheesy or spongy appearance on cut section. Microscopically, the villi of the small intestine are enlarged and infiltrated with large, pale-staining mononuclear cells with foamy cytoplasm. The normal architecture of the mesenteric lymph nodes is destroyed and the nodes assume a "Swiss cheese" appearance, with many large vacuoles filled with a sudanophilic material. The lymph nodes are also infiltrated with the characteristic mononuclear foam cells, which do not take up a stain for neutral fat but do give a positive reaction with the periodic-acid-Schiff stain for glycoproteins. Thirty-one

TABLE 1

Frequency of Clinical Findings in 54 Reported Cases

	Number Present	Number Absent	Number Not Recorded
Symptoms			
Diarrhea	51	0	3
Abdominal pain and distention	47	0	7
Weight loss	50	1	3
Arthralgia	36	8	10
Cough	14	0	40
Physical Findings			
Abdominal distention	47	0	7
Hypotension	40	3	11
Skin pigmentation	30	0	24
Doughy abdomen or palpable abdominal mass	25	0	29
Laboratory Findings			
Anemia	45	1	8
Increased fecal fat	20	4	30
Achlorhydria	17	6	31
Hypoproteinemia	13	10	31
Low glucose tolerance curve	13	6	35
Abnormal small bowel roentgenograms	24	4	26
Pathologic Findings			
Serositis	31	3	20
Cardiac valve vegetations	14	1	39

patients had evidence of recent or old inflammatory involvement of the pericardial, pleural or peritoneal surfaces, and 14 patients had vegetations on one or more of the cardiac valve cusps.

Differential Diagnosis: The striking picture of emaciation, weakness, diarrhea, hypotension and pigmentation of the skin strongly resembles Addison's disease, but this can be ruled out by serum sodium and potassium determinations and a normal Thorn test for adrenocortical function. The normal or flat glucose tolerance test, serum amylase determinations, and examination of the stools for meat fibers will help to differentiate chronic pancreatitis. The presence of hypochromic anemia and absence of glossitis will rule out primary sprue and idiopathic steatorrhea. Regional enteritis, chronic ulcerative colitis, amebic dysentery, and gastrocolic or enterocolic fistulae are ruled out by appropriate roentgenograms of the gastrointestinal tract, stool examinations and direct sigmoidoscopic visualization of the colon. Symptomatic sprue due to involvement of the mesenteric lymph nodes or obstruction of the thoracic duct or cisterna chyli by tuberculosis, lymphomata, sarcoidosis or nonspecific inflammatory involvement of these structures will have to be differentiated, but there may be evidence of the primary disease in other organs. Exploratory laparotomy and biopsy of the small intestine and mesenteric lymph nodes will establish the diagnosis after these other causes of diarrhea and steatorrhea are eliminated.

Pathogenesis: Whipple [1] recognized that the mononuclear foam cells did not contain fat, and thought that absorption of a toxic substance or abnormal type of fat was responsible for the reaction. Hill [7] first proposed the theory that the disease was due to mechanical obstruction of the lymph channels secondary to a chronic infectious process in the abdominal lymphatics. However, obstruction of the lymphatic channels is not an essential feature of Whipple's disease and is absent in most of the cases. Reinhart and Wilson [13] proposed the theory of increased intestinal excretion and re-absorption of fat, but this has not been substantiated. Clemmesen [19] felt that the disease was a pararheumatic inflammatory reaction which produced fibrosis and obstruction of the lymph channels. His patient had a history of rheumatic fever, and was the only one with a reported elevation of the antistreptolysin titer. Rosen and Rosen [26] and Chapnick [27] adhered to the theory of lymphatic channel obstruction. Kampmeier [33] suggested the relationship of Whipple's disease to the rheumatic group of diseases. Black-Schaffer [35] demonstrated that the material in the foam cells exhibited the characteristics of a glycoprotein, since it has been found to give a positive reaction with the periodic-acid-Schiff stain. Upton [50] confirmed Black-Schaffer's observations but suggested that the material was a substance secreted by the intestinal epithelial glands and faultily re-absorbed. However, he also noted that the substance could be related to the hexosamine of blood serum, which is elevated in collagen diseases. Jones and others [52] felt that the defect was a metabolic disturbance in the function of the intestinal mucosa, with adequate digestion but with some abnormality in absorption. They felt that the corticosteroids probably exerted some metabolic influence on the epithelial cells to improve absorption, thereby producing remissions. Story and Sagild's patient [53] had a marked elevation of the serum glycoproteins, which is also a finding in the collagen diseases. Cortisone had no effect on the course of their patient, and they suggested that it was probably not the adrenal steroid fraction that would be helpful in the disease, and recommended trial of adrenocorticotropin or hydrocortisone (Compound F).

Plummer [84] also noted the lack of beneficial response to cortisone, with a complete remission after treatment with adrenocorticotropin, and felt that the improvement was due to elaboration of steroids in the adrenal cortex other than cortisone.

The frequent occurrence of arthralgia, polyserositis or cardiac valvular lesions in patients with Whipple's disease, the findings of a positive stain for glycoprotein in the mononuclear foam cells in the intestinal mucosa or mesenteric lymph nodes, and the recent report of elevated serum glycoproteins in Whipple's disease all tend to incriminate Whipple's disease as being closely related to the rheumatic or collagen diseases. Further studies on future cases will be necessary to determine the exact etiology of this disorder, but it is heartening to note prolonged remission of symptoms with adrenocorticotropin therapy in a disease which previously had been almost uniformly fatal.

Summary

A 62 year old white male with Whipple's disease had a symptomatic remission after administration of adrenocorticotropin and cortisone. This is the fourth published report in which a favorable response to steroid therapy has occurred.

The literature has been reviewed, and the findings in 53 previously reported cases have been briefly summarized.

BIBLIOGRAPHY

1. Whipple, G. H.: A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues, Bull. Johns Hopkins Hosp. **18**: 382, 1907.
2. Blumgart, H. L.: Three fatal adult cases of malabsorption of fat, Arch. Int. Med. **32**: 113, 1923.
3. Fahr, T.: Zur Frage des Zusammenhanges zwischen Stoffwechselstörungen und morphologischen Veranderungen im reticuloendothelialen System, Klin. Wchnschr. **7**: 1787, 1928.
4. Fleischmann, R.: Ueber tumorbildende Fettgewebsgranulome im Gokörse des Dünndarms, Arch. f. klin. Chir. **158**: 692, 1930.
5. Collins, A. N., and Berdez, G. L.: Chyle cysts of mesentery, Arch. Surg. **28**: 335, 1934 (case 2).
6. Jarcho, S.: Steatorrhea with unusual intestinal lesions, Bull. Johns Hopkins Hosp. **59**: 275, 1936.
7. Hill, J. M.: Mesenteric chyladenectasis: report of a case, Am. J. Path. **13**: 267, 1937.
8. Boeck, in discussion on Bargen, J. A., Bollman, J. L., and Kepler, E. J.: Diarrhea of pancreatic insufficiency, Am. J. Digest. Dis. **4**: 728, 1938.
9. Gaertner, K.: Über einen Fall von hochgradiger Fettspeicherung in den Mesenteriallymphknoten, Frankfurt. Ztschr. f. Path. **52**: 529, 1938.
10. Glynn, L. E., and Rosenheim, M. L.: Mesenteric chyladenitis with steatorrhea and features of Addison's disease, J. Path. and Bact. **47**: 285, 1938.
11. Korsch, J. H.: Fettstoffwechselstorung mit Granulombildung in Mesenterium, Zentralbl. f. allg. Path. u. path. Anat. **71**: 337, 1938.
12. Kloos, K.: Ueber eine eigenartige Fettresorptionsstörung und ihre Beziehung zur Sprue, Virchows Arch. f. path. Anat. **304**: 625, 1939.
13. Reinhart, H. L., and Wilson, S. J.: Malabsorption of fat (intestinal lipodystrophy of Whipple): report of a case, Am. J. Path. **15**: 483, 1939.

14. Pearse, H. E.: Whipple's disease, or intestinal lipodystrophy, Surgery **11**: 906, 1942.
15. Sailer, S., and McGann, R. J.: Lipophagic granulomatosis of enteric tract, Am. J. Digest. Dis. **9**: 55, 1942.
16. Apperly, F. L., and Copley, E. L.: Whipple's disease (lipophagia granulomatosis), Gastroenterology **1**: 461, 1943.
17. Vaux, D. M.: Chyladenectasis with steatorrhea, J. Path. and Bact. **55**: 93, 1943.
18. Amsterdam, J. J., and Grayzel, D. M.: Intestinal lipodystrophy (lipophagia granulomatosis or Whipple's disease), Am. J. M. Sc. **210**: 605, 1945.
19. Clemmesen, J.: Steatorrhea arthro-pericarditica (mesenteric chyladenectasis): review and report of a case, Acta med. Scandinav. **121**: 495, 1945.
20. Escudero, P., Mosto, D., and Landabure, P.: Lipodistrofia intestinal de Whipple, Dia Méd. **17**: 915 (Aug. 27) 1945.
21. Fitzgerald, P. J., and Kinney, T. D.: Intestinal lipodystrophy (Whipple's disease), Am. J. Path. **21**: 1069, 1945.
22. Hansen, K., and van Staa, H.: Die einheimische Sprue und ihre Folgekrankheiten (sekundäre Avitaminosen), 1936, G. Thieme, Leipzig, p. 39, cited by Clemmesen in Acta med. Scandinav. **121**: 495, 1945.
23. Frei, R.: Über die histopathologischen Veränderungen am Dünndarm bei Störungen der Fettresorption (sog. Xanthomatose des Dünndarms), Schweiz. Ztschr. f. Path. u. Bakt. **10**: 685, 1947.
24. Oliver-Pascual, E., Galan, J., Oliver-Pascual, A., and Castillo, E.: Un caso de lipodistrofia intestinal con lesiones ganglionares mesenterica de granulomatosis lipofagia (enfermedad de Whipple), Rev. españ. enferm. ap. digest. y nutrición **6**: 213, 1947.
25. Pemberton, J. de J., Comfort, M. W., Fair, E., and Zaslow, J.: Intestinal lipodystrophy (Whipple's disease): preliminary report of three cases in early stage of disease, Surg., Gynec. and Obst. **85**: 85, 1947.
26. Rosen, M. S., and Rosen, S. H.: Intestinal lipodystrophy of Whipple: report of a case and analysis of literature, Am. J. Path. **23**: 443, 1947.
27. Chapnick, H. A.: Idiopathic steatorrhea, with report of a case of Whipple's disease, Ann. Int. Med. **29**: 549, 1948.
28. Fernandez Luna, D., and Latienda, R. I.: Lipodistrofia Generalizada, Rev. Asoc. méd. argent. **62**: 590, 1948.
29. Newman, B., and Pope, R. H.: A case of intestinal lipodystrophy (Whipple's disease) simulating Boeck's sarcoid, Gastroenterology **11**: 120, 1948.
30. Rutishauser, E., Demole, M., and Mach, R. S.: Sprue due to intestinal lipostasis (intestinal lipodystrophy; Whipple's disease), Rev. méd. de la Suisse Rom. **68**: 573, 1948.
31. Avery, J. F., and Paulley, J. W.: Intestinal lipodystrophy (Whipple's disease), Lancet **1**: 214, 1949.
32. Copland, S. M., Colvin, S. H., Essrig, I. M., and Heibner, W. C.: Intestinal lipodystrophy or Whipple's disease, Surgery **26**: 688, 1949.
33. Kampmeier, R. H., and Peterson, J. C.: Whipple's disease; its relationship to the rheumatic state, Tr. Am. Clin. and Climatol. A. **61**: 248, 1949.
34. Schutz, P. J., Benner, W. H., and Christian, W. A.: Intestinal lipodystrophy (Whipple's disease), Am. J. Med. **7**: 553, 1949.
35. Black-Schaffer, B.: Tinctorial demonstration of glycoprotein in Whipple's disease, Proc. Soc. Exper. Biol. and Med. **72**: 225, 1949.
36. Hendrix, J. P., Black-Schaffer, G., Withers, R. W., and Handler, P.: Whipple's intestinal lipodystrophy: report of 4 cases and discussion of possible pathogenic factors, Arch. Int. Med. **85**: 91, 1950.
37. Odessky, L., and Burdison, W. R.: Intestinal lipodystrophy (Whipple's disease) occurring with parathyroid hyperplasia and nephrosis; case with autopsy, Arch. Path. **49**: 307, 1950.

38. Plummer, K., Russi, S., Harris, W. H., Jr., and Caravati, C. M.: Lipophagic intestinal granulomatosis (Whipple's disease): clinical and pathologic study of 34 cases, with special reference to clinical diagnosis and pathogenesis, Arch. Int. Med. **86**: 280, 1950.
39. Reveno, W. S.: Intestinal lipodystrophy (Whipple's disease): report of a case, New England J. Med. **243**: 216, 1950.
40. Tracey, M. L., and Brolsma, M. P.: Whipple's disease (lipophagia granulomatosis); report of one case, Gastroenterology **15**: 366, 1950.
41. Palumbo, L. T., and Rugtiv, G. M.: Intestinal lipodystrophy (Whipple's disease), Arch. Surg. **62**: 604, 1951.
42. Albertini, B.: Contributo morfologico e clinico sulla lipodistrofia intestinale o morbo de Whipple, Arch. ital. mal. app. diger. **18**: 195, 1952.
43. Christie, A. C., and Dalton, D. A. G.: A fatal case of intestinal lipodystrophy of Whipple investigated during life, J. Path. and Bact. **64**: 351, 1952.
44. Inguscio, L.: Lipodistrophia intestinale o sindrome de Whipple, Athena **18**: 315, 1952.
45. Janowitz, H. D.: Personal communication.
46. Luton, E. F.: A possible cause of death in Whipple's disease, Gastroenterology **20**: 327, 1952.
47. Mendes De Leon, C., and Coenegracht, J.: Lipodystrophia intestinalis (ziekte van Whipple), Nederl. tijdschr. v. geneesk. **96**: 560, 1952.
48. Paulley, J. W.: A case of Whipple's disease (intestinal lipodystrophy), Gastroenterology **22**: 128, 1952.
49. Russo, R. R.: Whipple's disease: review of the literature and report of two cases, Arch. Int. Med. **89**: 600, 1952.
50. Upton, A. C.: Histochemical investigation of the mesenchymal lesions in Whipple's disease, Am. J. Clin. Path. **22**: 755, 1952.
51. Wallace, J. L.: Intestinal lipodystrophy, Whipple's disease, Texas State J. Med. **48**: 771, 1952.
52. Jones, C. M., Benson, J. A., Jr., and Roque, A. L.: Whipple's disease, New England J. Med. **248**: 665, 1953.
53. Story, R. D., and Sagild, U.: Whipple's disease (intestinal lipodystrophy) and serum glycoproteins, J. A. M. A. **152**: 312, 1953.
54. Plummer, K., Weisiger, B. B., and Caravati, C. M.: Successful corticotropin (ACTH) therapy of Whipple's disease refractory to cortisone, Arch. Int. Med. **91**: 784, 1953.

PHENYLBUTAZONE TOXICITY: REPORT OF A CASE OF ACUTE RENAL FAILURE*

By MORTIMER B. LIPSETT, M.D., *New York, N. Y.*, and RALPH GOLDMAN, M.D., *Los Angeles, California*

A hitherto unreported reaction to phenylbutazone will be presented in this report. The diagnosis of acute renal failure is supported by the course of the illness and a renal biopsy.

CASE REPORT

The patient was a 60 year old retired Army colonel who entered on September 24, 1953, complaining of inability to urinate for three days. He had been followed

* Received for publication December 22, 1953.
From the Veterans Administration Center, Los Angeles, California, and the Department of Medicine, University of California Medical Center, Los Angeles, California.

in the Arthritis Clinic of Wadsworth General Hospital for five years with diagnosis of mild rheumatoid and degenerative arthritis. During this period numerous blood counts, urinalyses and occasional serum creatinine and blood urea nitrogen determinations had been normal. He had no history suggestive of cardiovascular or renal disease, and there had been no symptoms referable to the urinary tract.

Three weeks before entry the patient took six 200 mg. tablets of phenylbutazone over a three-day period on the advice of his physician. He voluntarily discontinued these because of gastric irritation. The only other medications used in the past year were aspirin and Amphojel. Six days before entry he ingested another 200 mg. tablet of phenylbutazone. Two days later he was given 2 gr. of phenobarbital because of severe arthritic pain in his neck and shoulders. During that day he was drowsy and did not recall his urinary output. The following day he was able to void only a few drops of urine in spite of the forced intake of a quart of water. As the oliguria continued he again consulted his physician and was referred to this hospital. There was no history of recent ingestion or exposure to any known nephrotoxic agents, and during the week preceding entry there were no symptoms suggesting urinary tract disease.

Physical examination disclosed a well developed, obese white man who did not appear ill. His weight was 182 pounds, seven pounds heavier than his average weight. His pulse, blood pressure and temperature were normal. The rest of the physical examination, with the exception of minor arthritic deformities, was within normal limits.

He was catheterized on entry and 10 c.c. of urine containing red cells, white cells and broad and granular casts were obtained. The major laboratory findings are outlined in table 1. Other pertinent laboratory work included an albumin-globulin ratio of 3.6/2.0, normal electrocardiograms, normal serum bilirubin, and no evidence of hemoglobinemia or hemoglobinuria. The chest roentgenogram taken on entry showed minimal cardiomegaly and slight pulmonary vascular congestion.

On the second hospital day a renal biopsy of the left kidney was performed * (figure 1). This was done with a Vim-Silverman needle, using a flank approach. A cylinder of tissue was obtained without bleeding. Ten minutes following the procedure, however, the patient complained of severe pain in the biopsy area. Muscle rigidity was noted and his blood pressure dropped to 80/40 mm. of Hg. This responded to Neosynephrine and Levophed, and after five hours his pressure was

TABLE 1

	September							October				
	24	25	26	27	28	29	30	1	2	5	8	15
Output (c.c./24 hrs.)	35	90	160	325	640	1660	2350	2400				
Hematocrit (%)	—	28	19	21	23	24	23	27	—	28	28	31
Hemoglobin (gm.%)	—	9.9	6.7	7.0	8.4	8.7	8.6	8.0	—	9.5	9.5	11.8
BUN (mg.%)	76	119	124	—	134	—	—	130	112	78	66	15
Creatinine (mg.%)	—	6.7	—	—	10.8	10.8	10.4	9.4	7.3	3.0	2.3	1.3
CO_2 (mEq./L.)	—	12.3	14.1	—	13.7	13.7	—	18.0	—	21.0	—	19.8
Chloride (mEq./L.)	—	96	100	—	86	91	—	81	—	100	—	—
Sodium (mEq./L.)	—	142	—	—	124	134	—	130	—	146	—	—
Potassium (mEq./L.)	—	5.0	—	—	4.7	6.3	—	5.0	—	5.1	—	—
Weight (lb.)	182	184	—	184	183	181	180	176	173	170	166	166
Endogenous Creatinine Clearance (c.c./minute)							3.0	14	20	58	64	

* The authors wish to acknowledge the assistance of Dr. Joseph J. Kaufman in obtaining the renal biopsy.

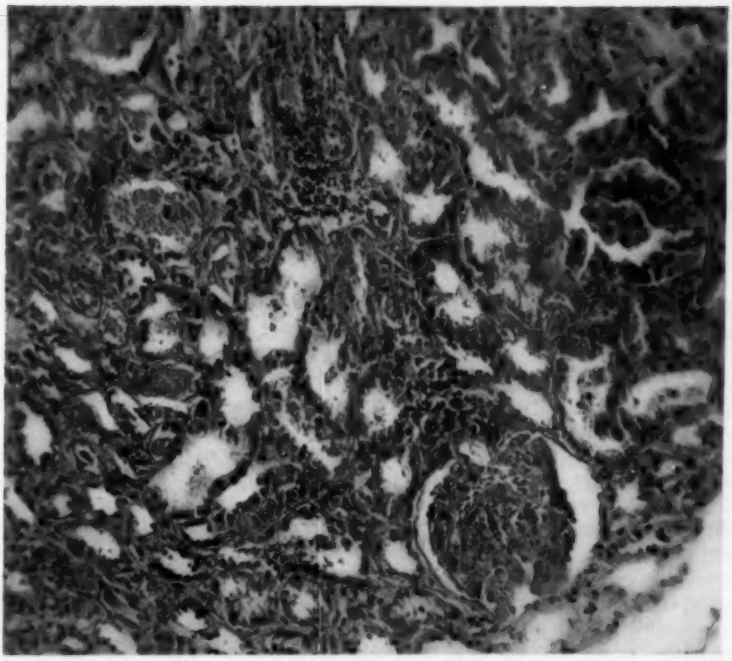


FIG. 1. Renal biopsy showing convoluted tubular necrosis with occasional intraluminal cast formation and capillary thrombi in the glomeruli.

stable without vasopressor agents. Later, the patient passed two 10 c.c. specimens of grossly bloody urine, but all subsequent urines were clear. Reëxamination during the succeeding days failed to reveal any large extravascular collection of blood. However, because of the coincidence of this episode with a falling hematocrit, he was given one pint of blood on each of the next two days. His subsequent clinical course was uneventful. He was maintained on a modified Kolff regimen,[1] and his oral intake of fluids was strictly controlled. Ambulation was started on his sixth hospital day and he was discharged after 22 hospital days.

Following recovery, an intravenous pyelogram was normal. However, an osteoblastic lesion of the ileum was noted in these films, and acid and alkaline phosphatases were 11.2 and 12.2 units, respectively. Reëxamination of the prostate suggested a small nodule near the apex. The patient was referred to the surgical service for follow-up of a probable prostatic carcinoma.

Of incidental interest was the observation that almost complete relief of arthritic symptoms accompanied this illness. Increased mobility of the wrists and fingers was also noted. With recovery from the acute renal disease the arthritic symptoms gradually recurred.

The discharge diagnoses were: (1) lower nephron nephrosis,* (2) carcinoma of the prostate with metastases; (3) rheumatoid arthritis, mild.

* The term "acute renal failure" is preferable, but is not coded in the Standard Nomenclature of Disease.

Comment

The occurrence of acute renal failure as a result of drug sensitization is an accepted phenomenon, and voluminous literature has accumulated. During the sulfonamide era it was recognized that many of the cases of acute renal failure could not be attributed to crystalluria and consequent urinary tract obstruction.[2] It was also noted that the blood level of the drug could not be correlated with the extent of the renal damage. It must be assumed that some individuals responded abnormally to amounts of the drug which do not usually produce untoward effects.

This case presents features that make it highly probable that renal failure was precipitated by phenylbutazone. The patient had been seen previously and renal function had been good. He was given phenylbutazone, a known sensitizing agent; there was an interval of three weeks, the drug was repeated, and oliguria appeared two to three days later. The course was that of a typical renal ischemic episode,[3] with recovery and almost complete return of renal function. The renal biopsy showed no evidence of chronic disease, and the pathologic features were those of acute renal failure.

We have recently observed another patient in whom phenylbutazone idiosyncrasy may have precipitated the final uremic episode. This patient was a young man with severe rheumatoid spondylitis of eight years' duration and a nephrotic syndrome due to secondary amyloidosis of two years' duration. His serum creatinine was normal less than two months before death. He was given phenylbutazone for three days, and on the third day the urine output dropped sharply and he entered the hospital. His serum creatinine had risen from 0.6 mg. per cent to 7.7 mg. per cent. The oliguria continued and the patient died three days later. At autopsy the kidneys were extensively involved with amyloid. This case may be analogous to some of those given sulfonamide drugs, cases in which oliguria and uremia followed the first few days of treatment,[2] and the syndrome could not be attributed to either crystalluria or sensitization. Although this patient's kidneys were severely damaged prior to phenylbutazone, there was a dramatic decrease in kidney function coincident with the phenylbutazone ingestion. However, an accelerated deterioration of kidney function in the interval between his last clinic visit and his final admission cannot be excluded.

Phenylbutazone has been reported to give rise to toxic manifestations involving all of the body systems.[4] Previously noted renal complications have been salt retention [5] and hematuria.[6] No instance of azotemia has yet been attributed to phenylbutazone. This report therefore calls attention to another serious complication of phenylbutazone therapy, emphasizing the need for caution in its use.

Conclusions

1. A case has been presented of acute renal failure probably attributable to phenylbutazone sensitization.

2. A second case was briefly noted in which phenylbutazone idiosyncrasy may have accelerated insufficiency in kidneys already severely damaged.

BIBLIOGRAPHY

1. Kolff, W. J.: Forced high caloric, low protein diet and the treatment of uremia, Am. J. Med. 12: 667, 1952.

2. Murphy, F. D., Kuzma, J. F., Polley, T. Z., and Grill, J.: Clinicopathologic studies of renal damage due to sulfonamide compounds, Arch. Int. Med. **73**: 433, 1943.
3. Oliver, J., MacDowell, M., and Tracy, A.: The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemuric episode, J. Clin. Investigation **30**: 1305, 1951.
4. Hemming, A., and Kuzell, W. C.: The pharmacologic and clinical characteristics of phenylbutazone (Butazolidin), Antibiotics and Chemotherapy **3**: 634, 1953.
5. Wilkinson, E. L., and Brown, H.: The effect of Butazolidin (phenylbutazone) on water and electrolyte excretion, Am. J. M. Sc. **225**: 153, 1953.
6. Patterson, R. M., Benson, J. F., and Schoenberg, P. L.: Clinical evaluation of Butazolidin in 32 cases of rheumatoid arthritis, U. S. Armed Forces M. J. **4**: 109, 1953.

HYPERTENSION ASSOCIATED WITH RENAL NEOPLASM: REPORT OF TWO CASES *

By ROBERT M. DOWBEN, M.D., *Philadelphia, Pennsylvania*

THE successful experimental production of hypertension by methods which cause unilateral renal ischemia has created an interest among clinicians in human cases of hypertension associated with unilateral renal disease. In such cases of hypertension, renal neoplasm is an unusual cause. Maher and Woiska [1] found two cases of renal tumors in a series of 101 cases of primary urinary tract disease associated with hypertension. In 29 cases of hypertension and unilateral renal disease, Abeshouse [2] reports three cases with neoplasm. In other series of cases [3-6] of hypertension associated with unilateral kidney disease, no cases of tumor appear. Two cases of renal neoplasm with elevated arterial tension are reported here in which the blood pressure returned to normal levels after nephrectomy.

CASE REPORTS

Case 1. A 57 year old housewife was admitted to the Medical Service of the Hospital of the University of Pennsylvania on August 7, 1946, for study of an abdominal mass found during a previous admission for biopsy and fulguration of a urethral polyp (Gynecology Service of Dr. Karl Bachman). She was asymptomatic save for a dull ache in the left abdomen when she tired. She did not have known hypertension before this admission.

On examination the pulse was 96, the blood pressure 200/118 mm. of Hg. The ocular fundi did not show abnormal changes. The heart was somewhat enlarged to the left. A normal sinus rhythm was present. A soft apical systolic murmur was heard. In the left abdomen a large, hard, irregularly knobby mass was felt which extended from the costal margin to the level of the iliac spine. The mass was nontender and moved with respiration. Laboratory studies showed a red blood count of 3.9 million, a hemoglobin of 10.2 gm. per cent, and a white blood count of 7,000, with a normal differential count. Examination of the urine was negative. X-ray examination of the chest demonstrated some cardiac enlargement and a small calcified mass in each hilum. A urogram showed the left kidney to be displaced downward and inward by an extrinsic soft tissue mass. An electrocardiogram was within normal limits.

* Received for publication November 23, 1953.
From the Department of Medicine, School of Medicine, University of Pennsylvania, and the Medical Clinic, Hospital of the University of Pennsylvania.

On the sixth hospital day a left nephrectomy was performed. The surgical specimen was a nodular tumor, 17 by 10 by 8 cm., arising from the upper central portion of the parenchyma of the left kidney. On cut section the tumor varied in color from light brown to deep purple, and contained many gelatinous cysts and necrotic areas. On microscopic examination (performed by Dr. A. E. Bothe), the tumor was a hypernephroma. The cells were large, with a clear cytoplasm and eccentric nuclei. Large blood vessels coursed through the tumor. There was no evidence of invasion of vessels by tumor.

Recovery was without event. The blood pressure returned to normal levels postoperatively. A typical reading on the fourteenth postoperative day was 130/80 mm. of Hg. On this day the hemoglobin was 10.2 gm. per cent and the white blood count 7,500, and the serum electrolytes were within normal limits.

The patient was well until March, 1953, when she presented herself to her family physician* with a rapidly growing tumor of the thyroid which proved to be a carcinoma of the thyroid. At this time her blood pressure was 200/120 mm. of Hg. She had some left heart enlargement, and her electrocardiogram showed a left ventricular strain pattern. She was last seen in August, 1953, with a blood pressure of 200/120 mm. of Hg, in good health and without signs of metastases from either the hypernephroma or the carcinoma of the thyroid.

Case 2. A 42 year old machinist was admitted to the Medical Service of the Hospital of the University of Pennsylvania on January 23, 1948, for study of hypertension. He had donated blood frequently during World War II, and on these occasions his blood pressure was said to have been normal. A normal blood pressure was recorded at the time of a life insurance examination one year before admission. Three months before admission an arterial tension of 190 mm. of Hg systolic was found when the patient consulted his physician about an upper respiratory infection. His blood pressure was 220/130 mm. of Hg two weeks before admission. The patient was asymptomatic, and the past medical inquiry was not contributory.

On examination the pulse was 92, the blood pressure 220/120 mm. of Hg. Examination of the ocular fundi revealed arteriolar spasm and narrowing of the vessels, particularly at the periphery. The heart was somewhat enlarged to the left. A normal sinus rhythm was present; there were no murmurs nor thrills. A few musical râles were heard in the chest. An abdominal mass was felt in the left upper quadrant which was nontender and did not move with respiration.

Laboratory studies showed the hemoglobin to be 14.5 gm. per cent and the white blood count 6,600. The blood urea nitrogen was 15 mg. per cent, the plasma proteins were 6.1 gm. per cent. A persistent hematuria was found on several urinalyses. A phenolsulfonphthalein excretion test showed 45 per cent dye excretion in the first 15 minutes and a total of 90 per cent excretion in two hours. An electrocardiogram showed only a sinus tachycardia. Slight left ventricular enlargement was found on fluoroscopy. A urogram revealed a soft tissue mass about 5 cm. in diameter at the upper pole of the left kidney. Nine grains of Sodium Amytal given orally over a three hour period resulted in a drop of blood pressure from a baseline level of 200/112 mm. of Hg to 146/84 mm. of Hg. An intravenous histamine test was negative.

The patient was explored operatively on the twelfth hospital day. A normal left adrenal was seen. A tumor mass was found to occupy the upper third of the left kidney. A partial nephrectomy was done at this time and three large nodes along the aorta beneath the psoas fascia were removed. On gross examination the tumor consisted of firm, whitish tissue containing multiloculated cysts, filled for the most part with clotted blood. Microscopically (microscopic examination by Dr. H. T. Enterline), the tumor consisted of large polygonal cells arranged in sheets, the cyto-

* I am indebted to Dr. Nathan L. Marcus, of Tampa, Florida, for a follow-up report on this patient.

plasm often containing eosinophilic granular material, with large, eccentrically placed, deeply staining nuclei. Rare mitotic figures were seen. The pathologic diagnosis was carcinoma of kidney, hypernephroid type.

Postoperatively a urinary fistula developed, and blood began to drain from the wound in increasing amounts. On the ninth postoperative day there was a profuse hemorrhage, followed by shock. On the following day a total nephrectomy was done. The second surgical specimen showed invasion of the renal vein by tumor.

Recovery from the second operation was uneventful. The blood pressure was recorded frequently and remained at a level around 130/70 mm. of Hg. At the time of the patient's discharge on the eleventh postoperative day the blood pressure was 140/90 mm. of Hg.

The patient was well and normotensive for the next five years. He was readmitted to the hospital on December 31, 1952, after the sudden onset of severe orbital headaches. He complained of nausea and vomited occasionally. On examination, positive findings were limited to the nervous system. The left eye was more prominent than its fellow and was more tense to palpation. The pupils were equal and reacted well. The extraocular movements were full. The fundi showed, in addition to minimal hypertensive changes, a slight papilledema and rippling of the optic radiations on the right. A slight left hemiparesis was present. There was no cardiac enlargement. The blood pressure was 150/88 mm. of Hg. Laboratory studies revealed a hemoglobin of 11.8 gm. per cent, a red blood count of 4.1 million, and a white blood count of 8,600, with a normal differential count. Urinalyses were negative. The blood urea nitrogen was 16 mg. per cent. A phenolsulfonphthalein excretion test showed 35 per cent dye excreted in 15 minutes and a total of 75 per cent in two hours. The alkaline phosphatase was 3 units. X-ray examination of the chest, abdomen and long bones was negative. X-rays of the skull showed the pineal to be markedly displaced to the left. An electroencephalogram showed right frontotemporal abnormalities.

In the hospital the headaches worsened and there ensued a rapid progression of neurologic signs and increase in the papilledema. On the tenth hospital day a right-sided craniotomy was performed. No tumor was located, so that only an external subtemporal decompression was done. Postoperatively the patient gradually deteriorated, and died three months after the second admission.

The family limited postmortem examination to the head. A right sided, massive, organizing, intracerebral hemorrhage was found. No tumor tissue was seen.

Discussion

An association of hypertension and hypernephroma was first noted by Neusser[7] in 1898. In a series of 491 cases of tumor of the kidney, Morlock and Horton[8] found that 45 per cent of the hypernephroma cases and 42 per cent of the cases of other renal tumors had hypertension. In no instance was any postoperative drop in blood pressure noted. These authors felt that the incidence of hypertension was not significantly high. Braasch, Walters and Hammer[9] reported 38 instances of hypertension (27.7 per cent) in a series of 137 adenocarcinomas of kidney.

A causal relation between unilateral renal disease and hypertension is clearly established when the arterial tension falls to normal levels after nephrectomy. In 21 hypertensive cases of Braasch, Walters and Hammer,[9] where the postoperative as well as the preoperative blood pressures were followed, the blood pressure in nine cases returned to normal. An interesting case of hypertension and hypernephroma was described by Horton.[10] The blood pressure returned to normal after nephrectomy, but became elevated again with the reappearance of a

metastasis of the original tumor years later. Linder [11] reported five cases of adenocarcinoma of kidney with hypertension; in three of these, the blood pressure returned to normal postoperatively. Abeshouse [2] reported two cases of hypernephroma and a case of papillary adenocarcinoma, all with hypertension which was relieved after nephrectomy. A case of papillary adenocarcinoma with hypertension was reported by Irazu.[12] The arterial tension returned to normal after nephrectomy.

Wilms' tumors may also be accompanied by hypertension. Bradley and Pincoffs [13] reported five cases of Wilms' tumor with hypertension. In two of these cases the blood pressure fell after removal of the tumor but became elevated again with the reappearance of the tumor. In contrast to these cases, Koons and Ruch [14] described the case of a seven year old girl with Wilms' tumor and hypertension. The normal blood pressure after nephrectomy persisted despite the existence of tumor metastases in other parts of the body. Daniels [15] studied 18 cases of Wilms' tumor and found a moderate elevation of blood pressure in six and an appreciable elevation in eight.

The mechanism by which the hypertension is produced in these cases is not clear. The early German authors [7, 16] believed that the tumors produced a pressor substance analogous to adrenalin. This view is consistent with the notion that a hypernephroma is a tumor of suprarenal anlage. The common occurrence of fever, increased pulse rate and telangiectases with hypernephromas may support this concept.[17] In addition, one may point to the case [10] in which the hypertension returned with the appearance of metastases of the original tumor.

Probably more important is the role of ischemia in the production of hypertension. Abeshouse [2] pointed out that ischemia may arise because of compression of the renal vessels, or by torsion of the vessels by renal displacement, by infiltration of the renal parenchyma by tumor, or by thrombosis of the renal vessels. Not unusually, kidney tumors contain large areas of necrosis, as was the case in both of the patients reported here. In the second case, a tumor thrombus of the main left renal vein was present. In this case tests for pheochromocytoma were negative. A case described by de Sola Pool [18] may be cited here, in which an elevation in blood pressure appeared suddenly together with metastatic involvement of the kidneys by lymphosarcoma. The author felt that the mechanism in her case was compression of the renal parenchyma.

Ischemia becomes an attractive mechanism in view of the experimental methods of producing hypertension. Partial obstruction of the arterial circulation,[19] obstruction of the renal vein [20] and renal compression [21] are all means of producing hypertension in the experimental animal.

It is interesting to note that in both cases reported here the onset of hypertension was sudden and the course was one of rapid progression. This has been observed with frequency in cases of renal hypertension.[6] In the first reported case, hypertension appeared some years after nephrectomy without evidence of recurrence of tumor. The recurrence of the hypertension presumably is not associated with the previous episode of hypertension.

Summary

Two cases of hypernephroma with hypertension are presented in which the blood pressure returned to normal levels after nephrectomy. The possible

mechanisms are discussed in the light of experimental methods of producing hypertension. In one case, a tumor thrombus of the renal vein might have had a causal relation to the elevated blood pressure.

BIBLIOGRAPHY

1. Maher, C. C., and Woiska, P. H.: Urologic hypertension, J. Urol. **41**: 893, 1939.
2. Abeshouse, B. S.: Hypertension and unilateral renal disease, Surgery **10**: 147, 1941.
3. Nesbit, R. M., and Ratliff, R. K.: Hypertension associated with unilateral renal disease, J. A. M. A. **116**: 194, 1941.
4. Sensenbach, W.: Effect of unilateral nephrectomy in treatment of hypertension, Arch. Int. Med. **73**: 123, 1944.
5. Kittredge, W. E., and Brown, H. G.: The present status of unilateral renal hypertension, J. Urol. **55**: 213, 1946.
6. Perera, G. A., and Haelig, A. W.: Clinical characteristics of hypertension associated with unilateral renal disease, Circulation **6**: 549, 1952.
7. Neusser, E.: Die Erkrankungen der Nebennieren, *in* Nothnagel, H., Spec. Path. u. Ther. **18**: 71, 1898.
8. Morlock, C. G., and Horton, B. T.: Variations in systolic blood pressure in renal tumor: a study of 491 cases, Am. J. M. Sc. **191**: 647, 1936.
9. Braasch, W. F., Walters, W., and Hammer, H. J.: Hypertension and the surgical kidney, J. A. M. A. **115**: 1837, 1940.
10. Horton, T. T.: The relationship of hypertension to renal neoplasm, Proc. Staff Meet., Mayo Clin. **15**: 472, 1940.
11. Linder, F.: Über blutdrucksteigernde Nierentumoren, Klin. Wchnschr. **25**: 498, 1947.
12. Irazu, J.: Adenoma papilar de rinon hipertension renal, Rev. argent. de urol. **15**: 69, 1946.
13. Bradley, J. E., and Pincoffs, M. C.: The association of adenomyo-sarcoma of the kidney (Wilms' tumor) with arterial hypertension, Ann. Int. Med. **11**: 1613, 1938.
14. Koons, K. M., and Ruch, M. K.: Hypertension in a 7 year old girl with Wilms' tumor relieved by nephrectomy, J. A. M. A. **115**: 1097, 1940.
15. Daniels, W. E.: The hypertensive factor in Wilms' tumor, South. M. J. **32**: 1014, 1939.
16. Federoff, S. P.: Ueber Befund von Adrenalin in einem Nierentumor (Hypernephrom), Folia urolog. **2**: 551, 1908.
17. Braasch, W. F., and Griffin, M.: The prognosis in renal carcinoma, J. A. M. A. **106**: 1343, 1936.
18. de Sola Pool, N.: Hypertension due to perirenal constriction, J. Mt. Sinai Hosp. **13**: 188, 1946.
19. Goldblatt, H.: Experimental hypertension induced by renal ischemia, Harvey Lectures **14**: 523, 1938.
20. Pedersen, A. H.: A method of producing experimental chronic hypertension in the rabbit, Arch. Path. **3**: 912, 1927.
21. Page, I. H.: A method for producing persistent hypertension by cellophane, Science **89**: 273, 1939.

EDITORIAL

TRANSMISSIBILITY OF LEUKEMIA

THE etiology of leukemia is an unsolved problem which has stimulated much study and speculation. Leukemia resembles malignant neoplasms in many obvious ways, and it has come to be regarded by most students as essentially a neoplastic process. Recent work, on the other hand, has emphasized the possibility that a living (infectious) agent may be concerned. These views, indeed, are not irreconcilable nor mutually exclusive. The occurrence of a disease closely resembling human leukemia not only in chickens and related birds but also in mice has made extensive experimental studies possible.

That leukemia in chickens can be transmitted in the laboratory to uninfected subjects was shown by Ellermann and Bang nearly 50 years ago.[1] Their observations have been amply confirmed. The disease can be transmitted in series and maintained indefinitely by the injection of cell-free filtered extracts which contain an agent having the properties of a filterable virus. The disease, however, was not transferred promptly by contact from one chicken to another, they were not able to demonstrate how the infection was conveyed under natural conditions, and considerable skepticism arose as to the significance of the supposed virus.

Lymphomatosis is a relatively common fatal disease in chickens, characterized by the production of lymphoid tumors, extensive infiltration of the organs and eventually invasion of the circulating blood by the abnormal cells. It causes heavy losses in the poultry industry, so funds have been available and much time has been expended in its study. Recent work by the group at the Agricultural Experiment Station in East Lansing, Michigan, has been especially informative. Susceptibility varies in different races and strains of hens, depending upon genetic, hormonal and environmental factors and the age of the host, as well as the presence of the agent. Waters [2] has reported a careful study of a susceptible strain of white Leghorn hens with a high incidence of spontaneous leukemia. Hatching eggs were placed in newly built quarters, and the chickens were raised under a strict quarantine which for a period of eight years kept out "all common infections" except lymphomatosis and all parasites except coccidiosis. Lymphomatosis first appeared after 40 days and eventually from 20 to 40 per cent of the birds developed the disease. As there was no extraneous source of infection, except conceivably the exterior of the egg shells, they concluded that infection must have been transferred from the parent to the chick in the egg.

In further experiments they established individual families of one cock and one hen, hatching and rearing the chicks under strict isolation. Lymphoma-

[1] Ellermann, V., and Bang, O.: Experimentelle Leukämie bei Hühnern, Centralbl. f. Bakt. I Abt. Orig. **46**: 595–609, 1908.

[2] Waters, N. F.: The contagious nature of a lymphoid tumor in chickens, Science **106**: 246–248, 1947 (Sept. 12).

tosis appeared in nine such families, but in 13 it did not. A family of one cock and four hens, selected from one of the negative families, produced a large progeny. Of 91 of these chicks which were kept on isolation, none showed lymphomatosis. Of 121 siblings of these 91, returned immediately to the general population, 32 per cent developed lymphomatosis. Infection in these chicks was obviously by direct contact. They found that very young chicks readily acquired such infection, but that susceptibility diminished rapidly with age and after 30 days it was but slight.[3]

Gross [4] has also reported observations supporting the view that infection is transmitted from one generation to the next through the egg. The tissues of freshly hatched chicks contain the virus. It may be transmitted by an infected hen which never develops lymphomatosis herself, and in fact at least two consecutive generations may be skipped, the disease again appearing in the third.

The evidence is clear that lymphomatosis in chickens is due to a transmissible agent which has the characteristics of a filterable virus. It also seems clear that the agent is transmitted from one generation to the next in the egg, remaining latent until the chick has reached adult age, although direct transmission by contact is also possible, at least to very young chicks of susceptible strains. Birds and mammals are rather remotely related, however, and leukemia in mammals might behave differently.

The type of mammalian leukemia which has been most adequately studied is that occurring in mice. It has been known for many years that under suitable conditions the disease can be transferred from mouse to mouse by inoculation (transplantation) of intact leukemic cells, which proliferate in the new host. The earlier attempts to transfer the disease by the injection of filtered extracts were not successful. As in the case of chickens, susceptibility varies greatly with the strain of mice employed. This work has been greatly facilitated by the development of inbred strains selected on the basis of their susceptibility. In one such line developed by Furth, known as the AK strain, leukemia developed spontaneously in from 70 to 85 per cent of the mice at ages from seven to 14 months. Mice from such a line afford a dependable source of leukemic material, but their value as experimental subjects is obviously limited. It was fortunate that other strains of mice were found, such as the C3H strain, in which leukemia very rarely develops spontaneously but which are susceptible to inoculation under suitable experimental conditions.

The work was also helped indirectly by the observations of Bittner [5] and others [6] regarding mammary carcinoma of mice, which in its behavior

[3] Waters, N. F., and Bywaters, J. H.: Influence of age of chickens at contact exposure on incidence of lymphomatosis, Poultry Science **28**: 254, 1949.

[4] Gross, L.: The "vertical" transmission of mouse mammary carcinoma and chicken leukemia, Cancer **4**: 626–633, 1951.

[5] Bittner, J. J.: The causes and control of mammary cancer in mice, Harvey Lect. Series 42, 221–246, 1946–47.

[6] Gross, L.: The vertical epidemic of mammary cancer in mice, Surg., Gynec. and Obst. **88**: 295–308, 1949.

resembles leukemia in many ways. These tumors develop in mice which are infected in infancy by an agent in their mother's milk. This "milk agent" has the characteristics of a filterable virus. It is also found in the tumors, in the mammary glands, and in most of the other tissues of the infected mouse. Adult mice are resistant, but young suckling mice are highly susceptible (up to 90 per cent of the females) by either the oral or parenteral route, although they show no evidence of infection (no tumor) until they become adults and have had one or more pregnancies. Infected mice transmit the agent to the young in the milk before they develop a tumor. If, however, the young are removed immediately after birth and nursed by a mouse of an uninfected line, the young do not become infected, and the line of cancer will die out. Infected mice may transfer the agent to their offspring without ever developing a tumor themselves. In this way one and even two successive generations may be skipped, the tumor reappearing in the third.

The transmissibility of leukemia in mice has been studied particularly by Gross,[7] who has recently summarized his views. If a cell suspension from leukemic tissue of a spontaneously diseased mouse (AK strain) is inoculated into other healthy mice of the same line, regardless of age acute leukemia will develop in a large percentage within about three weeks and be speedily fatal. If such inoculations are made into a different susceptible strain (C3H), the adults are usually resistant. There is considerable strain specificity in adult mice as far as harboring heterologous cells is concerned. A large proportion of suckling mice, however, quickly develop fatal leukemia. In these instances, the leukemia is presumably due to proliferation of the cells which were inoculated, and the cells of the host take little if any part.

If such suspensions are centrifuged until intact cells and other coarse material are removed, the supernate does not as a rule cause the prompt development of acute leukemia. In a leukemia-free strain like C3H, adult mice are again resistant. Suckling mice, preferably under 12 hours old, show no immediate response, but a large proportion develop acute leukemia as adults, and up to 50 per cent of their offspring may eventually show it.[8] In this way, a new leukemic strain of mice may be initiated.

Suspensions of intact leukemic cells from such mice can be inoculated readily into adult mice of the same strain (C3H), producing a local tumor and acute leukemia promptly, but not as a rule into healthy adult AK mice. The cells behave, therefore, as if they arose from cells of the host and not from any stray cells of the donor (AK) strain which might have been harbored since infancy in a latent state.[9]

Although the agent of leukemia can be transferred to infant mice by inoculation, there is no evidence that it can be conveyed by direct contact. It

[7] Gross, L.: Is leukemia caused by a transmissible virus? A working hypothesis, Blood **9**: 557–573, 1954.

[8] Gross, L.: Pathogenic properties and "vertical" transmission of the mouse leukemia agent, Proc. Soc. Exper. Biol. and Med. **78**: 342–348, 1951.

[9] Gross, L.: Biologic properties of the mouse leukemia agent, Cancer **6**: 153–158, 1953.

is not conveyed by the milk. Gross believes that it is transferred "vertically" from parent to young through the germinal cells, remaining dormant or in an inactive form throughout the greater part of the life of the animal. As in the case of mammary carcinoma, an infected female may pass the agent of leukemia to her young without herself ever developing the disease. At least two generations may be so skipped, leukemia eventually reappearing in the third generation. He has reported the production of leukemia by the injection into C3H mice of extracts of tissues of normal embryos [10] and of ovaries and testes of healthy young adults of the leukemic AK strain.[11]

In earlier experiments Gross reported that the agent was filterable (Seitz filter),[8] although only 9 of 32 mice inoculated developed leukemia. Most of his work was done with centrifugalized extracts, in which there is at least a theoretical possibility that intact leukemic cells might be present. Furth [12] questioned Gross' conclusions on the ground that his experimental series were too small and that the presence of intact cells in his extracts was not adequately excluded. Gross has since reported confirmatory experiments with larger numbers of mice and has also reported the transmission of the agent in Berkefeld filtrates, although only 10 of 45 mice developed leukemia.[13]

The only direct confirmation from other sources which the reviewer has found is by Stewart,[14] who reported successful transmission to new born hybrid mice (one parent from a "low" and one from a "high" leukemic strain) by filtrates of leukemic tissue (from AK strain). She obtained only a small percentage of "takes," however, when precisely following Gross' procedures.

In conclusion, there is strong evidence that this form of leukemia in mice as well as the mammary carcinoma of mice is caused by a transmissible agent with the properties of a filterable virus. Evidence is also strong that it is conveyed from parent to offspring in or with the germinal cells, but further confirmation from other laboratories is still desirable. Failure to obtain this promptly, however, need not be surprising. The agent can operate only if conditions are favorable—conditions determined by genetic, hormonal and environmental factors, many of which probably are not adequately understood. It may well be difficult in other laboratories to duplicate adequately the conditions under which Gross' experiments were conducted.

[10] Gross, L.: Spontaneous mouse leukemia developing in C3H mice following inoculation in infancy with AK leukemic extracts or AK embryos, Proc. Soc. Exper. Biol. and Med. **76**: 27–32, 1951.

[11] Gross, L.: Presence of leukemia agent in normal testes and ovaries of young mice of AK line, Acta Haemat. **10**: 18–26, 1953.

[12] Furth, J.: Analytical review: Recent studies of the etiology and nature of leukemia, Blood **6**: 964–975, 1951.

[13] Gross, L.: Neck tumors or leukemia developing in adult C3H mice following inoculation in early infancy with filtered (Berkefeld N) or centrifugated (144,000 × g) AK-leukemic extracts, Cancer **6**: 948–957, 1953.

[14] Stewart, S. E.: Leukemia in mice produced by a filterable agent present in AK leukemic tissues with notes on a sarcoma produced by the same agent, Anat. Rec. **117**: 532, 1953 (Abst.)

Whether these observations also apply to leukemia in man is now pure speculation, although the mouse is a nearer relative than the chicken. The earlier uniformly unsuccessful attempts to transmit the disease to human volunteers now appear quite inappropriate and inconclusive, and the use of infants in imitation of the successful animal experiments is obviously impossible. The frequency of familial cases of leukemia is probably greater than would be expected from purely random distribution, but it is still low and not very impressive. To obtain information which would make possible valid conclusions on the basis of the incidence of the disease would require observation of many families over at least a century. A new approach to the problem is needed.

If this analogy should prove valid, it would indicate wide spread distribution of the agent, with a very low incidence of activity and long periods of latency in terms of "skipped" generations. This would seem, on the whole, to be discouraging from the standpoint of prevention as well as effective therapy of the disease.

PAUL W. CLOUGH

REVIEWS

Anatomy of the Human Body ("Gray's Anatomy"). 26th Ed. By HENRY GRAY, F.R.S., Late Fellow of the Royal College of Surgeons; edited by CHARLES MAYO GOSS, M.D., Managing Editor of the *Anatomical Record*. 1480 pages; 17.5 × 26.5 cm. Lea & Febiger, Philadelphia 6, Pa. 1954. Price, $16.00.

This text which has been so popular among students and clinicians for nearly a century has become even more useful and valuable under the skillful editorship of Dr. Charles M. Goss of Louisiana University School of Medicine. Changes in the sequence of material, rearrangement of plates, the addition of numerous illustrations and a much-needed revision of portions of the text combine to render the book more effective and helpful than ever before. The introduction to the subject, now more complete, is followed by the section on embryology which places greater emphasis on human material than heretofore and employs some of the beautiful photographs of early human embryos published by Hertig and Rock. The section on surface and topographical anatomy now receives greater prominence as the second instead of the final chapter of the book. The heart has been lifted from the section on development and histology of the vascular system and is considered in a separate chapter. Illustrations have been borrowed from more recent sources in many cases and include, for example, an electron photomicrograph of the lung. New drawings from the cadaver at a magnification of five times replace some of the older, inadequate diagrams of tissues. They fill a need for illustrations in the "borderline area of anatomy" between those structures which are visible to the unaided eye and those which require the use of the microscope.

In the preceding edition the major revision involved the muscles; in this twenty-sixth edition the editor has carefully rewritten the chapter on the peripheral nervous system to integrate time-honored descriptions with the results of recently published research. Sixteen new plates in color from the atlas of Töndury have been added to this section. Headings, subheadings and numbering make the nerves and their ramifications easier to follow. A chart of the cranial nerves and their functional components has been introduced. The section on the autonomic system has been greatly expanded.

The nomenclature is based on the BNA terminology except in a few cases where the BR or INA represent a distinct improvement. The editor has wisely discouraged the perpetuation of eponyms by employing the more useful and meaningful terminology wherever possible. Valuable additions are the carefully selected lists of references, grouped by subject, which have been appended to each chapter. These contain references to both classical papers and to numerous recent works. They should stimulate the interest of the student in further and more specialized reading especially since, in many instances, they will bring to his attention the works of his own teachers.

Dr. Goss, his associates and the publishers are to be complimented upon this splendid new edition of Gray's Anatomy.

VERNON E. KRAHL

Heart Disease and Industry, with Particular Reference to Workmen's Compensation Cases. By MEYER TEXON, M.D., New York City. 324 pages; 17.5 × 26 cm. Grune and Stratton, Inc., New York. 1954. Price, $7.50.

The problem of trauma, effort and emotional strain and its relationship to subsequent cardiac disability has long been clouded by conclusions based on the impression that there is a causal relationship between effort and heart disease. The purpose

of this book is to provide medical criteria for determining causal relationship between trauma and heart disease, and to render assistance to referees and medical boards by providing factual data helpful in reviewing controversial medical evidence. In order to establish such scientific criteria, the author has critically analyzed one hundred consecutive Workmen's Compensation cases involving heart disease. The entire group is coded uniquely so that problems involved and the cases in which they occur with particular significance are accessible for detail study. This is coupled with a complete and searching survey of the recent literature concerning the pathogenesis of coronary occlusion and myocardial infarction. The lack of significance of effort as a factor in the production of coronary thrombosis is critically analyzed. From his study the author concludes "that only in the rarest of instances, and even these are of doubtful scientific validity, can a causal relation be established between effort and coronary thrombosis. The chronologic relation of effort to clinical evidence of acute coronary thrombosis cannot be accepted as scientific proof of causal relation."

Other types of heart disease are discussed. With each case is a detailed account concerning the prognosis, disability and reasoning behind the author's opinion regarding the pathogenesis of the heart disease. Rehabilitation is discussed in a brief manner.

This book is written skillfully and with clarity. As an aid to interested parties with no medical background, all scientific terms are grouped in an index and glossary. This volume should be provocative reading for both the medical and legal profession. A reasonably sound foundation has been laid by the work of the author. It should serve as the basis for clarity in problems dealing with the medicolegal aspects of heart disease.

Because of existing inconsistencies in present customs and practices concerning litigation of industrial accidents, this work is recommended reading to those who would have at heart the best interest of the employer-employee relationship.

F. J. B.

The Uncommon Heart Diseases. By NATHANIEL E. REICH, M.D., F.A.C.P., Clinical Assistant Professor of Medicine, State University of New York, College of Medicine. 516 pages; 16 × 24.5 cm. Charles C. Thomas, Springfield, Illinois. 1954. Price, $10.50.

This book is intended to supplement the standard cardiac texts by covering "the uncommon and obscure yet interesting cardiopathies." In a text with this goal, the reader would look for a more detailed discussion, and a more recent and complete bibliography than the standard texts would permit. A great many subjects are included, and the presentation is clear and concise, but too often superficial. The list of selected references contains no articles or books more recent than 1949, except for several by the author in 1951 and 1952. This volume nevertheless should be of interest to the cardiologist.

S. S.

A Primer of Cardiology. 2nd Ed. By GEORGE E. BURCH, M.D., F.A.C.P., Henderson Professor of Medicine, Tulane University School of Medicine. 339 pages; 16 × 24 cm. Lea & Febiger, Philadelphia. 1953. Price, $5.50.

This is the second edition of a book intended as an introduction to cardiology. The co-author in the first edition was Dr. P. B. Reaser. This volume has many diagrammatic illustrations, and basic physiology is emphasized. There is too little clinical discussion, and there are a number of unqualified clinical statements which may be misleading to the inexperienced physician or student, for whom this volume is intended. This reviewer gets the impression that this book represents an effort to

salvage a good first edition by patching here and adding there; the quality of the resulting product is not uniform. This text is not the best available for the purpose.

S. S.

Multiple Myeloma. By I. SNAPPER, M.D., Director of Medical Education, Cook County Hospital, Chicago, Illinois; LOUIS B. TURNER, M.D., Research Assistant in Medicine, Mt. Sinai Hospital, New York, N. Y.; and HOWARD L. MOSCOVITZ, M.D., Resident, Second Medical Service, Mt. Sinai Hospital, New York, N. Y. 168 pages; 15.5 × 23.5 cm. Grune & Stratton, Inc., New York City. 1953. Price, $6.75.

For a number of years there has been need of a comprehensive text devoted to the subject of myelomatosis. The monograph created by Snapper, Turner, and Moscovitz appears to answer the need and contributes a great deal toward better understanding of a rather complicated subject.

The book is made up of 12 chapters of varying lengths and a well written final chapter which is actually a summary of the outstanding points of the preceding sections. The statistical features, symptomatology, diagnostic criteria and efficacy of the several modes of therapy of multiple myeloma are discussed. In addition, the senior author has drawn from his large experience with myeloma and created a particularly informative section devoted to the metabolic changes occurring in myelomatosis. Such personal experiences greatly enhance the value of the monograph as do the many illustrative charts, the representative x-ray reproductions and pathological sections appearing in both color and black and white. A brief bibliography and subject index appear at the end of the book.

The monograph is highly recommended to interested readers, as a classic in its field.

J. B. W.

Living with a Disability, at Home, at Work, at Play. By HOWARD A. RUSK, M.D., Director, The Institute of Physical Medicine and Rehabilitation, and EUGENE J. TAYLOR, in collaboration with MURIEL ZIMMERMAN, O.T.R., and JULIA JUDSON, M.S., The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center. 207 pages; 22 × 14 cm. The Blakiston Company, Inc., Garden City, New York. 1953. Price, $3.50.

The pictures on the jacket, by Bill Meek, seem more suggestive to me of the quality of this book than the title, *Living with a Disability, at Home, at Work, at Play.* The title suggests something on the order of *Mastering Your Disability,* by Harold A. Littleton, recently published, on the personal disability of a cord injury. Dr. Rusk's book really comprises by far the most superbly developed catalogue of usable, tested, pictured, pertinent devices and plans for use among the disabled, in largely urban relationships in homes, at work, in recreation and the arts. The line drawings and numbered, listed photographs make much information immediate, free, accessible.

The chapter on materials, uses, care, tensions appeals to one's inventive skills. What does the patient want? What are his wishes? provokes the winning total approach.

This totality is reflected in chapters on self-care devices, grooming problems, clothes and pocket-book designs, transportation, plans for apartments and bathrooms, kitchens, garages, workshops, with heights, holds, balances carefully estimated. Suction grips and springs, easy clothes fasteners, designs and arrangements challenge fresh inventions and also the efficiency of much we accept as normal.

Hobbies, music and other arts, recreations, even smoking, become possibilities with small aids.

Disabilities among rural populations and occupations exist. Much in this book is applicable, but generally it is a field open to further research.

"Mechanical Aids for the Disabled" as a title would seem to me to indicate more truly the content of the book.

All associated with the disabled will be intrigued with the suggestive quality of the book. Professionals immediately need it. Inventors will be stimulated. All disabled will be challenged by it; all normal persons doubly challenged, having done so little with so much. The efficiencies of the normals are always a matter of research, perhaps especially to the disabled. It is a fairly open field from their viewpoint.

Dr. Rusk and his brilliant team of co-authors are to be congratulated no less than the N. F. I. P. Bellevue Institute, the veterans and all individuals who have released ideas for others, including the contributions for the research from N. F. I. P. and the Disabled Homemakers' Research Fund.

G. E. S.

BOOKS RECEIVED

Books received during September are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Administrative Medicine: Transactions of the Second Conference, December 8, 9 and 10, 1953, Princeton, N. J. Edited by GEORGE S. STEVENSON, M.D., National and International Consultant, National Association for Mental Health, New York, N. Y. 164 pages; 24 × 16 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.00.

Biochemical Determinants of Microbial Diseases. Harvard University Monographs in Medicine and Public Health Number 13. By RENÉ J. DUBOS, The Rockefeller Institute for Medical Research. 152 pages; 21.5 × 14 cm. 1954. Harvard University Press, Cambridge. Price, $3.50.

Biochemical Investigations in Diagnosis and Treatment. By JOHN D. N. NABARRO, M.D., M.R.C.P., Assistant Physician, Middlesex Hospital, etc. 299 pages; 22.5 × 15 cm. 1954. H. K. Lewis & Co., Ltd., London. Price, 25s net.

Cirrhose und Narbenleber: Entstehung, Klinik und Therapie. By PROF. DR. MED. HEINZ KALK. 143 pages; 25.5 × 16.5 cm. (paper-bound). 1954. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 21.–; ganzleinen DM 23.–

Clinical Aspects of the Autonomic Nervous System. By L. A. GILLILAN, Ph.D., M.D., Associate Professor of Anatomy, Graduate School of Medicine, University of Pennsylvania. 316 pages; 22 × 15 cm. 1954. Little, Brown and Company, Boston. Price, $6.50.

Diagnosis and Treatment of the Acute Phase of Poliomyelitis and Its Complications. Edited by ALBERT G. BOWER, M.D. 257 pages; 23.5 × 15.5 cm. 1954. The Williams & Wilkins Company, Baltimore. Price, $6.50.

Emotions and Bodily Changes: A Survey of Literature on Psychosomatic Interrelationships, 1910–1953. 4th Ed. By FLANDERS DUNBAR, M.D., Med.Sc.D., Ph.D. 1,192 pages; 24 × 16 cm. 1954. Columbia University Press, New York. Price, $15.00.

Expert Committee on Venereal Infections and Treponematoses; Subcommittee on Serology and Laboratory Aspects: Third Report. World Health Organization

Technical Report Series No. 79. 52 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U.S.A. from Columbia University Press, International Documents Service, New York. Price, 50 cents.

Fundamentals of Internal Medicine. 4th Ed. By WALLACE MASON YATER, A.B., M.D., M.S. (IN MED.), F.A.C.P., Director, Yater Clinic, Washington, D. C., etc.; this edition prepared with the assistance of WILLIAM FRANCIS OLIVER, B.S., M.D., A.A.C.P., Staff Member, Department of Medicine, Santa Barbara Clinic, etc. 1,276 pages; 25.5 × 17.5 cm. 1954. Appleton-Century-Crofts, Inc., New York. Price, $13.50.

Galen of Pergamon. Logan Clendening Lectures on the History and Philosophy ot Medicine, Third Series. By GEORGE SARTON. 112 pages; 22 × 14 cm. 1954. University of Kansas Press, Lawrence, Kansas. Price, $2.50.

Legal Medicine, Pathology and Toxicology. 2nd Ed. By THOMAS A. GONZALES, M.D., Chief Medical Examiner of the City of New York (Retired), etc.; MORGAN VANCE, M.D., Deputy Chief Medical Examiner of the City of New York, etc.; MILTON HELPERN, M.D., Chief Medical Examiner of the City of New York, etc.; and CHARLES J. UMBERGER, Ph.D., Toxicologist, Office of the Chief Medical Examiner of the City of New York, etc.; Introduction by HARRISON S. MARTLAND. 1,349 pages; 26 × 17.5 cm. 1954. Appleton-Century-Crofts, Inc., New York. Price, $22.00.

Liver Injury: Transactions of the Twelfth Conference, September 21, 22 and 23, 1953, Princeton, N. J. Edited by F. W. HOFFBAUER, M.D., Associate Professor, Department of Medicine, University of Minnesota Hospitals, Minneapolis, Minn. 231 pages; 24 × 15.5 cm. 1954. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.25.

Symposium on Problems of Gerontology: Proceedings of a Symposium Held Under the Auspices of The Johns Hopkins University, School of Hygiene and Public Health and The National Vitamin Foundation, Incorporated, New York City, March 2, 1954. Nutrition Symposium Series Number 9. By F. H. BETHELL, B. F. CHOW, C. S. DAVIDSON, H. J. DEUEL, JR., D. J. INGLE, J. E. KIRK, A. I. LANSING, C. N. H. LONG, H. A. RAFSKY and N. W. SHOCK. 141 pages; 23 × 15.5 cm. (paper-bound). 1954. The National Vitamin Foundation, Incorporated, New York. Price, $2.50.

Unsere Erfahrungen über die moderne Behandlung der Miliartuberkulose und der Meningitis tuberculosa im Kindesalter. By J. R. WEBER and K. KÜMIN; with a preface by PROF. DR. ED. GLANZMANN. 96 pages; 23.5 × 16.5 cm. (paper-bound). 1954. Verlag Hans Huber, Bern. Price, Fr. 12.80.

The Year Book of Medicine (1954–1955 Year Book Series). Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., FRANZ J. INGELFINGER, M.D., and PHILIP K. BONDY, M.D. 711 pages; 20 × 13.5 cm. 1954. The Year Book Publishers, Incorporated, Chicago. Price, $6.00.

COLLEGE NEWS NOTES

An Experiment in Postgraduate Medical Program by Television

On Thursday evening, September 23, 1954, from 6:00 p.m. to 7:00 p.m., Eastern Daylight Saving Time, the American College of Physicians presented the first coast-to-coast, closed-circuit Postgraduate Medical Symposium on The Management of Hypertension, the project being supported financially by the Wyeth Laboratories of Philadelphia. The panel of distinguished physicians included, in addition to Dr. Cyrus C. Sturgis, President of the College who presided, Professor F. H. Smirk, F.R.A.C.P., of the University of Otago, Dunedin, New Zealand, Dr. Garfield G. Duncan, F.A.C.P., Director of the Medical Division, Pennsylvania Hospital, Philadelphia, Dr. R. W. Wilkins, F.A.C.P., Chief of the Hypertension Clinic, Massachusetts Memorial Hospital, Boston, and Dr. E. D. Freis (Associate), Adjunct Clinical Professor of Medicine, Georgetown University School of Medicine, and Chief of Medicine at the Veterans Administration Hospital, Washington, D. C. It was first announced that the program would be telecast to 23 receiving stations across the United States, but demands were so pressing that the original plan was extended to include a special receiving station at the Sherman Hotel, Chicago, exclusively for the convention of the Mississippi Valley Medical Association, an outlet at the Municipal Auditorium at Louisville particularly for the Kentucky State Medical Association convention there, and a receiving station at Miami for the State of Florida. A tally of the attendances indicates a total attendance of 8,307 although it is believed that a larger number was in attendance in some cities than was recorded by registration. The cities at which the largest attendance was recorded were Chicago (two stations), 875; Philadelphia, 750; New York, 600; Memphis, 550; Washington, 525; Los Angeles, 460; San Francisco, 425; Pittsburgh, 400; Colorado Springs, Houston and Louisville, 300 each.

At the end of the Telecast a transcript of the entire proceedings, along with a brief evaluation questionnaire, was handed to each attendant. Many hundreds of these questionnaires are being returned to the College Headquarters; it will require considerable time to tabulate the results. It is, however, impressively evident that this program met with universal approval, appreciation and enthusiasm. It is also evident that it is almost the universal opinion that such programs must be restricted to closed-circuit telecast even though that involves the necessity of physicians reporting to central receiving stations. A host of suggested titles for further programs has been submitted.

Perhaps no other postgraduate medical experiment has appealed so much to the imagination of the members of the College and to the public press. Reports appeared in the newspapers all over the nation; telegrams of appreciation and congratulations were received from medical societies and individual physicians. This experiment, it should be remembered, was organized and put on without the benefit of prior experience by the College and the participants. One could not estimate in advance the seating facilities required nor the general attitude of the medical profession toward the receipt of the program. The results have been gratifying, yet with this preliminary experience, and from the advice and suggestions of the members, the College can greatly improve these televised programs in case they are continued and funds are made available.

To provide a wider distribution of the material presented in the Telecast, Wyeth Laboratories has had made a kinescopic reproduction of the program which is available to medical institutions and societies. Requests for this service should be made to Wyeth Laboratories, 1401 Walnut St., Philadelphia, Pa.

A.C.P. Postgraduate Courses

By the time of the appearance of this issue of the Annals, eight of the A.C.P. Postgraduate Courses on the Autumn semester will have been concluded, with only Course No. 9 yet to be given—A Survey of Recent Developments in the Cardiovascular Field, under the direction of Dr. Louis N. Katz, F.A.C.P., Michael Reese Hospital, Chicago, Ill., December 6–11.

The registration for the College courses has been significantly higher in the autumn of 1954 than for corresponding periods in the last few years. There were a number of new courses directed by new men and given for the first time at new institutions. Course No. 1, Selected Problems in Internal Medicine, directed by Dr. Wann Langston, F.A.C.P., at the University of Oklahoma, had a registration of over 50; Course No. 2, Basic Concepts in Internal Medicine, directed by Drs. Charles M. Caravati, F.A.C.P., and Kinloch Nelson, F.A.C.P., at the Medical College of Virginia, had a maximal registration of nearly 100; Course No. 3, Newer Developments in Cardiovascular Diseases, directed by Drs. Arthur M. Master, F.A.C.P., and Charles K. Friedberg, F.A.C.P., at the Mount Sinai Hospital, New York City, had a registration of over 150; Course No. 4, Medical Aspects of Neoplastic Diseases, directed by Drs. Cornelius P. Rhoads, F.A.C.P., and Rulon W. Rawson, F.A.C.P., at the Memorial Center for Cancer, New York City, had a registration of over 50; Course No. 5, Selected Subjects in Internal Medicine, directed by Drs. Roy R. Snowden, F.A.C.P., and Frank J. Gregg, F.A.C.P., at the University of Pittsburgh, a limited course, had a registration of 25; Course No. 6, Physiological Basis for Internal Medicine, directed by Dr. Julius H. Comroe, F.A.C.P., at the University of Pennsylvania Graduate School of Medicine, had a registration of over 100; Course No. 7, Internal Medicine, directed by Dr. Herrman L. Blumgart, F.A.C.P., at Beth Israel Hospital at Boston, had a maximal registration of 75, and Course No. 8, Gastro-Enterology, directed by Henry L. Bockus, F.A.C.P., at the University of Pennsylvania Graduate School of Medicine, approached the maximal registration of 100.

The A.C.P. Committee on Postgraduate Courses and the Board of Regents, will announce the specific Postgraduate Course program for the first half of 1955 in the December issue of this journal. The contemplated courses were announced in the October issue.

A.C.P. Regional Meetings

Since the 1954 Annual Session of the College in Chicago, the following Regional Meetings have been conducted. Some of these meetings are in areas of fairly small A.C.P. membership communities, but it should be emphasized that the College exists for minorities as well as for majorities. The same attention is accorded to small states as to large states, and their programs are in no sense less important or inferior to those in the thickly populated areas. As a matter of fact, percentage of member attendance is always greater in these smaller communities because there are fewer conflicting medical activities going on.

Northern California and Nevada—San Francisco, June 16, 1954; attendance, 168. Governor, Stacy R. Mettier, M.D.; Special Guest, Dwight L. Wilbur, M.D., Regent.

West Virginia—White Sulphur Springs, Aug. 19, 1954; attendance, 60. Governor, Paul H. Revercomb, M.D.; Special Guest, C. C. Sturgis, M.D., President, A.C.P.

North Dakota—Bismarck, Sept. 11, 1954; attendance, 46. Governor, Robert B. Radl, M.D.; Special Guest, C. C. Sturgis, M.D., President.

MONTANA-WYOMING—Butte, Mont., Sept. 15, 1954. Governor, Harold W. Gregg, M.D.; Special Guest, Dwight L. Wilbur, M.D., Regent.

ARKANSAS-OKLAHOMA—Oklahoma City, Oct. 8–9, 1954. Governors, Wann Langston, M.D., and A. A. Blair, M.D.; Special Guest, M. A. Blankenhorn, M.D., 1st Vice President.

MIDWEST (Ill., Ind., Iowa, Minn., Wis.)—Indianapolis, Ind., Oct. 9, 1954. Governor and General Chairman, James O. Ritchey, M.D., Ind.; Special Guests, C. C. Sturgis, M.D., President, Walter L. Palmer, M.D., Regent, and E. R. Loveland, Executive Secretary.

SOUTHEASTERN (Ala., Fla., Ga., La., Miss., S.C., Cuba)—Edgewater Park, Miss., Oct. 15–16, 1954. Governor and General Chairman, D. O. Wright, M.D., Ala.; Special Guest, William D. Stroud, M.D., Treasurer, A.C.P.

KENTUCKY—Lexington, Oct. 16, 1954. Governor, Sam A. Overstreet, M.D.; Special Guest, Wallace M. Yater, M.D., Regent.

NEW MEXICO—Albuquerque, Oct. 20, 1954. Governor, Robert Friedenberg, M.D.; Special Guest, Philip S. Hench, M.D., Regent.

NEW ENGLAND (Conn., Maine, Mass., N.H., R.I., Vt., Atlantic Provinces, Quebec)—Hartford, Conn., Oct. 22–23, 1954. Special Guests, C. C. Sturgis, M.D., President, and E. R. Loveland, Executive Secretary.

WESTERN PENNSYLVANIA—Pittsburgh, Oct. 27, 1954. Governor, C. Howard Marcy, M.D.; Chairman, Roy R. Snowden, M.D.; Special Guest, E. R. Loveland, Executive Secretary.

NEW JERSEY—Newark, Nov. 3, 1954. Governor, Edward C. Klein, Jr., M.D.; Special Guests, C. C. Sturgis, M.D., President, George H. Lathrope, M.D., 2nd Vice President, E. R. Loveland, Executive Secretary, George Morris Piersol, M.D., Former President and Former Secretary-General, and College Governors of adjoining states.

NORTHWEST (Idaho, Ore., Wash., Alta., B.C.)—Seattle, Wash., Nov. 4, 1954. Governor and General Chairman, George H. Anderson, M.D.; Local Chairman, Edwin G. Bannick, M.D.

WESTERN NEW YORK—Syracuse, Nov. 19, 1954. Governor, Edward C. Reifenstein, Sr., M.D.; Special Guests, C. C. Sturgis, M.D., President, and E. R. Loveland, Executive Secretary.

Future scheduled Regional Meetings:

MICHIGAN—Grand Rapids, Dec. 4, 1954. Governor, H. Marvin Pollard, M.D.; Special Guest, C. C. Sturgis, M.D., President.

NORTH CAROLINA—Durham, Dec. 9, 1954. Governor, Elbert L. Persons, M.D.; Program Chairman, Kenneth D. Weeks, M.D., Rocky Mount.

DELAWARE—Wilmington, Feb. 5, 1955. Governor, Lemuel C. McGee, M.D.; Chairman, Lewis B. Flinn, M.D.

SOUTHERN CALIFORNIA—San Diego, Feb. 12–13, 1955. Governor, Leland Hawkins, M.D.; Program Chairman, Roy A. Ouer, M.D., San Diego; Chairman of Arrangements, Samuel J. McClendon, M.D., San Diego; Special Guests, George F. Strong, M.D., President-Elect, Vancouver, and E. R. Loveland, Executive Secretary.

VIRGINIA—Richmond, Feb. 24, 1955. Governor, Charles M. Caravati, M.D.; Special Guest, C. C. Sturgis, M.D., President.

NEBRASKA—Omaha, Feb. 26, 1955. Governor, J. D. McCarthy, M.D.

SOUTHERN ILLINOIS—Peoria, March —, 1955. Governor, Charles H. Drenckhahn, M.D.; Local Chairman, James W. Sours, M.D., Peoria.

KANSAS—Wichita, March 18, 1955. Governor, William C. Menninger, M.D.; Local Chairman, Walter L. Schafer, M.D., Wichita.

New Life Members

The following Fellows of the College have become Life Members since the publication of the last list in the August issue of this journal:

Dr. Paul H. Morton, Coronado, Calif.
Dr. D. Schuyler Pulford, Sacramento, Calif.
Dr. Stanley L. Levin, Danville, Ill.

The College Life Membership Plan is an equitable and practicable arrangement by which a member may pay his dues during the productive years when his income is greatest, thus avoiding the burden of dues later in life. Life Membership offers security in advancing years against misfortune that often necessitates relinquishment of one's most cherished professional memberships because of the burden of dues.

The Life Membership fee entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual and Regional Sessions, to the *Annals of Internal Medicine*, etc. Each Life Member receives a framed certificate and his name is inscribed in the Life Membership Roll at the College. Life Members are active members for life. All Life Membership fees are deposited in the permanent Endowment Fund of the College and thus contribute to the security of the College as well as to the security of its members. The Life Membership fee is deductible on Federal income tax returns.

Gifts to College Library of Publications by Members

The College is pleased to announce that the following books have been presented by member authors to the College Library of Publications by Members:

Harold Rifkin, M.D., F.A.C.P., New York City—*Diabetic Glomerulosclerosis—The Specific Renal Disease of Diabetes Mellitus*, with Louis Leiter, M.D., Ph.D., and James Berkman, M.D.

William S. Hoffman, M.D., F.A.C.P., Chicago, Ill.—*The Biochemistry of Clinical Medicine*.

Roberto F. Escamilla, M.D., F.A.C.P., San Francisco, Calif.—*Laboratory Aids in Endocrine Diagnosis*.

Frank Howard Richardson, M.D., F.A.C.P., Black Mountain, N. C.—*The Nursing Mother—A Guide to Successful Breast Feeding*.

Papers for 1955 Meeting of the American Trudeau Society

The American Trudeau Society, the Medical Section of the National Tuberculosis Association, is now inviting the submission of papers for the 1955 annual meeting to be held in Milwaukee, Wis., May 23–27. Abstracts, which should be limited to a 300-word summary of papers offered for presentation, should be submitted in duplicate before Jan. 1, 1955, with an absolute deadline of Feb. 1, 1955, to David T. Carr, M.D., F.A.C.P., Chairman, Medical Sessions Committee, 200 First St., S.W., Rochester, Minn. Specific instructions concerning the preparation of abstracts and additional details concerning the papers accepted for presentation may also be obtained from Dr. Carr.

1955 European Rheumatology Congress

The Third European Rheumatology Congress will be organized by the Nederlandse Vereniging van Rheumatologen and will be held June 13–17, 1955, at Scheveningen, The Hague, Netherlands, under the auspices of the Ligue Européenne

contre le Rhumatisme. The Congress will be held at the Kurhaus, Scheveningen, with the scientific program composed of sections on rheumatic fever, connective tissue, osteo-arthritis of the spine and disc degeneration, and rheumatism and social medicine. Correspondence concerning further details should be addressed to Dr. H. van Swaay, Secretary of the Congress, Pieter Bothstraat 12, The Hague, Netherlands.

Coming Examinations by Certifying Boards

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis.

The written examination will be held Oct. 17, 1955, in major centers throughout the United States and the European and Far East Commands. The final date for filing applications is May 1, 1955.

The following oral examinations have been scheduled:

New Orleans, La.—Feb. 1–4, 1955
Philadelphia, Pa.—May 4–5, 1955
Washington, D. C.—May 6–7, 1955
Portland, Ore.—Sept. 14–16, 1955
Chicago, Ill.—Nov. 30—Dec. 2, 1955.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Oral Examination: New Haven, Conn.—Dec. 3–5, 1954.

American Trudeau Society Fellowships

The American Trudeau Society, Medical Section of the National Tuberculosis Association, provides a limited number of resident fellowships to promote the training of clinicians, medical teachers and administrators in the field of tuberculosis and related pulmonary diseases. Awards are open to citizens of the United States for work within this country. Candidates should hold the degree of Doctor of Medicine and preference will be given to those not more than 30 years of age.

Awards are made for graduate study in internal medicine, with emphasis on diseases of the chest, in an approved hospital. The American Board of Internal Medicine will accept one such year as part of the prerequisite training for certification in internal medicine and in pulmonary diseases.

All awards are determined by individual circumstances and are paid directly to the Fellow on a monthly basis. Fellowships are granted for one year. Not more than two renewals will be considered. Fellowship applications must be received by Feb. 1, 1955. Appointments may begin on any date at the convenience of the applicant, who may elect the hospital in which he wishes to study and the staff member who will supervise his work.

A few fellowships at a higher level of training and award are offered to specially qualified candidates who have been assured of a continued teaching appointment upon completion of training. Trudeau Fellowships are awarded for one year but may be renewed up to a total period of four years.

Further particulars concerning Resident and Trudeau Fellowships may be obtained on request to the Director of Medical Education, American Trudeau Society, c/o The Henry Phipps Institute, 7th and Lombard Sts., Philadelphia 47, Pa.

New Civil Service Commissions Available

New examinations have been announced by the U. S. Civil Service Commission for filling Medical Officer positions in certain Federal agencies as follows: Positions

of Medical Officer, paying $5,940 and $7,040 a year, and Medical Officer (Specialist), paying $8,360 to $10,800 a year, will be filled in various agencies in Washington, D. C., and vicinity, and in the U. S. Public Health Service and the Children's Bureau, located throughout the United States. Positions of Medical Officer, paying $7,425 to $10,450 a year, will be filled in the Panama Canal Company-Canal Zone Government Organization in the Panama Canal Zone.

Full information regarding these positions is given in Announcement No. 415 for Medical Officer, Announcement No. 414(B) for Medical Officer in the Panama Canal Zone, and Examining Circular EC-27 for Medical Officer (Specialist). These notices may be consulted at most post offices or copies may be secured direct from the U. S. Civil Service Commission, Washington 25, D. C.

Fellowships Available from National Foundation for Infantile Paralysis

The National Foundation for Infantile Paralysis announces the availability of a limited number of clinical fellowships for physicians interested in rehabilitation as it relates to their particular specialties.

The purpose of these fellowships is to provide an opportunity for physicians to study the concept and basic techniques of total rehabilitation. It is the responsibility of the candidate to arrange a program of study which places emphasis on rehabilitation in relation to his individual clinical specialty.

Applicants are eligible for these fellowships if they have graduated from an approved school of medicine, have completed not less than one year of internship and one year of approved resident training in one of the medical specialties in an approved hospital, are licensed to practice medicine in one or more states, are U. S. citizens (or have made application for citizenship), and are in sound health.

Financial awards are based on the individual need of each applicant and may include tuition, if any, and a monthly stipend for maintenance. The stipends range from $300 to $400 per month, depending upon marital status and the number of dependents.

Also available are a limited number of postdoctoral fellowships in medicine and the related biological sciences.

These fellowships, which generally are for a period of one to three years, are offered to candidates who are preparing for careers in scientific research and/or academic medicine. They are not awarded to investigators for the support of a research project. Special consideration will be given to applicants interested in such fields as: microbiology, biochemistry, biophysics, orthopedics, pediatrics, neurology and epidemiology. Eligibility requirements include: an M.D., Ph.D., or equivalent degree, U. S. citizenship (or application for citizenship) and sound health.

Stipends ranging from $3,600 to $7,000 a year are allowed, the specific sum being determined by marital status and number of dependents. The institution in which the Fellow receives his training may request compensation of $500 to $1,000 a year.

Selection of all candidates will be made on a competitive basis by the National Foundation's Fellowship Committee. For consideration by the Fellowship Committee in February, 1955, applications for both types of fellowships must be received by Dec. 1, 1954; for consideration in May, 1955, applications must be filed by March 1, 1955; for consideration in November, 1955, by Sept. 1, 1955.

For further information and application blanks address: The National Foundation for Infantile Paralysis, Division of Professional Education, 120 Broadway, New York 5, N. Y.

Panels Conducted by Certifying Boards

The American Board of Proctology has initiated Panel Meetings on Proctology. Three such Panel Meetings were conducted at the Philadelphia County Medical Society headquarters on September 23, 1954. Invitations were issued to the medical profession generally.

A course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital by Louis N. Katz, M.D., F.A.C.P., Richard Langendorf, M.D., F.A.C.P., and Alfred Pick, M.D. This is an *advanced* course intended only for experienced electrocardiographers. The class will meet daily from 9:00 a.m. to 5:00 p.m., December 13–16.

Further information and a copy of the lecture schedule may be obtained from Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

The American Board of Dermatology and Syphilology has recently published a 36-page booklet of questions taken from recent written examinations, comprehensive in scope. It is available for $1.00 from the office of the Board at 129 E. 52nd St., New York 22, N. Y.

Bound Copy of *Bulletin on Rheumatic Diseases* Available to Physicians

The first four volumes of *The Bulletin on Rheumatic Diseases* have been bound in soft cover and are now available to physicians.

The Bulletin, published by the Arthritis and Rheumatism Foundation, is issued nine times a year and is available without charge to all physicians and medical students who request it.

Physicians wishing regularly to receive *The Bulletin on Rheumatic Diseases* at no cost should write to Dr. Russell L. Cecil, F.A.C.P., Medical Director, Arthritis and Rheumatism Foundation, 23 W. 45th St., New York 36, N. Y.

The bound special volume composed of all issues of *The Bulletin* of the past four years, is available from the Arthritis Foundation at the cost of $1.00.

Dr. Richard A. Kern, F.A.C.P., Secretary General of the American College of Physicians, gave the first Annual John Walker Moore Lecture to the student body of the University of Louisville School of Medicine, to internes, residents, faculty members and practicing physicians in the area at the opening of the current academic year. The Lecture, entitled, "The Physician and the Growing Problems of Suicide," was given in the Rankin Amphitheater. Dr. William K. Keller, F.A.C.P., recited briefly the background of the late Dr. John Walker Moore, F.A.C.P., and the reasons for the establishment of the Lectureship. The hall, seating 400, was filled to overflowing.

Dr. Russell H. Oppenheimer, F.A.C.P., has retired as Professor of Medicine at Emory University School of Medicine, Atlanta, and has moved to Jacksonville, Fla.

Dr. Howard T. Karsner, F.A.C.P., Washington, D. C., was honored at the recent annual meeting of the National Board of Medical Examiners in Philadelphia "for his leadership in the broad field of medical education." Dr. Karsner, who is Research Advisor to the Surgeon General of the Navy, received a scroll presented as an "expression of gratitude and appreciation . . . by his friends on the Board." During his 24 years as a member of the Board, Dr. Karsner has served as Chairman of the Examination Committee and as President.

Col. Joseph H. McNinch, (MC), USA, (Associate), has recently been awarded an Oak Leaf Cluster to the Legion of Merit for his services in Japan. Col. McNinch, who is the new Commander of the Army Environmental Health Laboratory, Edgewood, Md., was cited for "displaying outstanding professional skill and forceful leadership in an extensive program for the prevention and control of disease within the Far East Command."

Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, has been elected Second Vice President of the American Radium Society.

Dr. J. Lamar Callaway, F.A.C.P., Durham, N. C., was elected Secretary of the American Dermatological Association at its annual meeting earlier this year.

Dr. Samuel Donner, F.A.C.P., Hartford, has recently been elected President of the Connecticut Diabetes Association, and Drs. Burdette J. Buck, F.A.C.P., and Marvin B. Day (Associate), Hartford, and Sidney E. Eisenberg, F.A.C.P., New Britain, are members of the Council.

Drs. J. Will Fleming, Jr. (Associate), Moberly, and F. Stanley Morest, F.A.C.P., Kansas City, have recently been elected President and Secretary, respectively, of the Missouri Heart Association. Drs. A. Graham Asher, F.A.C.P., and A. Morris Ginsberg, F.A.C.P., both of Kansas City, are members of the Board of Directors.

Dr. E. E. Menefee, Jr., F.A.C.P., Durham, and Dr. C. D. Thomas, F.A.C.P., Black Mountain, were reëlected President and Vice President, respectively, of the North Carolina Trudeau Society at its recent Seventh Annual Meeting.

Dr. Leon S. Smelo, F.A.C.P., Birmingham, Ala., and Dr. Sidney Davidson, Lake Worth, Fla., have recently been appointed by the American Diabetes Association as Governors for their respective states.

Dr. Alvin E. Murphy, F.A.C.P., Palm Beach, was recently installed as President of the Florida Heart Association.

At the annual meeting of the American Heart Association, Dr. Carter Smith, F.A.C.P., Atlanta, College Governor for Georgia, was reëlected Secretary of the Section on Clinical Cardiology, and Dr. R. Bruce Logue, F.A.C.P., Atlanta, was reëlected for a three-year term as a member of the Association's Board of Directors.

Dr. George E. Burch, Jr., F.A.C.P., New Orleans, has recently been appointed a member of the National Advisory Heart Council. This Council, which is composed of fifteen leaders in the fields of medicine, science, education, and public affairs, reviews requests from individuals and non-federal institutions for grants in research and teaching.

Dr. Emma Sadler Moss, F.A.C.P., New Orleans, was chosen President-Elect of the American Society of Clinical Pathologists at the association's meeting in Washington, D. C., Sept. 6.

Dr. Harold G. Trimble, F.A.C.P., Oakland, Calif., was the official representative of the American College of Physicians to the Third International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the American

College of Chest Physicians, and presented under the patronage of the Spanish Government in Barcelona, Spain, October 4–8, 1954.

Dr. George F. Strong, President-Elect of the American College of Physicians, Vancouver, B. C., was the official representative of this College at a meeting of the Royal College of Physicians and Surgeons of Canada at Winnipeg, Manitoba, October 22–23, 1954.

Dr. Heinz R. Landmann, F.A.C.P., Santa Fe, N. M., left on October 3, 1954, for an extended medical tour of South America. On October 6, he delivered an address on "La Importancia de la Educacion Integral en la Medicina" at the University of Antioquia, Medellin, Colombia. He has appointments also in Quito, Ecuador; Lima, Peru; Santiago, Chile; and Buenos Aires, Argentina.

Four members of the College contributed to the annual meeting of the American Hospital Association in Chicago, Sept. 13–16. Dr. Norman S. Moore, F.A.C.P., Ithaca, N. Y., participated in a panel discussion, "Improving Our Face-to-Face Relationships," and Dr. Jack Masur (Associate), Washington, D. C., was moderator of the panel "A Hospital Is Ready for Accreditation—Or Is It?" Dr. Masur, who is Assistant Surgeon General, Chief, Bureau of Medical Services, Public Health Service, also discussed good medical records, and Dr. LeRoy H. Sloan, F.A.C.P., Chicago, immediate Past President of the College and Vice Chairman of the Board of Commissioners of the Joint Commission, spoke on other hospital services. Dr. Howard A. Rusk, F.A.C.P., New York City, talked on the needs and distribution of care for the chronically ill.

With Dr. Jonathan C. Meakins, M.A.C.P., Montreal, Canada, as President, the Interstate Postgraduate Medical Association of North America held its annual International Medical Assembly in Minneapolis, Minn., Nov. 1–4. Dr. Meakins' Presidential Address, delivered at the Assembly Dinner on Nov. 3, was entitled "The Physician's Responsibility to the Aging Population." Other speakers and their topics included Dr. William S. Middleton, M.A.C.P., Madison, Wis., "Collagen Disturbances Encountered in General Practice"; Dr. Lewis M. Hurxthal, F.A.C.P., Boston, "Recent Developments in Endocrinology"; Dr. J. Arnold Bargen, F.A.C.P., Rochester, Minn., "Ulcerative Colitis in Children"; Dr. Frederick W. Madison, F.A.C.P., Milwaukee, College Governor for Wisconsin, "Purpura—Clinical Evaluation and Management"; Dr. Paul S. Rhoads, F.A.C.P., Chicago, "The Medical Management of Urinary Tract Infections"; Dr. Karver L. Puestow, F.A.C.P., Madison, Wis., "The Conservative Treatment of Stenosing Diseases of the Esophagus"; Dr. Charles W. Crumpton (Associate), Madison, Wis., "Prognosis in Mitral Stenosis"; and Dr. L. O. Underdahl (Associate), Rochester, Minn., "Male Hypogonadism." Dr. John S. L. Browne, F.A.C.P., Montreal, Canada, conducted a clinic, "Adrenal Cortex and Its Relation to Disease."

Drs. Cornelius P. Rhoads, F.A.C.P., New York City, William H. Sebrell, Jr., F.A.C.P., Bethesda, Md., and Nathan S. Kline (Associate), Orangeburg, N. Y., were among those who addressed the Bicentennial Conference of the Columbia University College of Pharmacy. Their respective topics were "Pharmacy's Challenge in the Problem of Cancer," "The Role of Drugs in Nutrition," and "The Pharmaceutical Approach to Mental Diseases." The Conference, which celebrated the 200th Anniversary of Columbia and the 125th of the College of Pharmacy, was held on the University campus in New York City on Oct. 14–15.

The Second Annual Symposium Day on Diabetes, "Vascular Disease in Diabetes Mellitus," was held Oct. 14 in New York City at the Memorial Center for Cancer and Allied Diseases and was sponsored by the Clinical Society of the New York Diabetes Association. Out-of-state speakers and their subjects included Dr. Alexander Marble, F.A.C.P., Boston, "Coronary Artery Disease in the Diabetic"; Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., "Prevention of Vascular Disease in the Diabetic"; Dr. Henry B. Mulholland, F.A.C.P., Charlottesville, Va., President of the American Diabetes Association, "The Management of the Diabetic with Vascular Disease." Dr. Herbert Pollack, F.A.C.P., New York City, President of the New York Diabetes Association, delivered the closing remarks and Dr. F. W. Williams, F.A.C.P., New York City, Retiring Chairman of the Clinical Society, gave the welcoming remarks. Dr. Irving Graef, F.A.C.P., New York City, presided at the morning session.

Dr. Walter B. Martin, F.A.C.P., Norfolk, Va., President of the American Medical Association, discussed "The County Society, Its Responsibilities and Duties" at the First Interstate Scientific Assembly, sponsored jointly by the Medical Society of the District of Columbia and the Medical Society of Virginia, and held in Washington, D. C., Nov. 1–3. Also participating in the program were Dr. Alexander Marble, F.A.C.P., Boston, who spoke on "Lente Insulin in the Treatment of Diabetes"; Dr. Charles A. Ragan, Jr., F.A.C.P., New York City, who discussed "The Present Management of Arthritis"; Dr. E. C. Bartels, F.A.C.P., Boston, whose topic was "The Medical Treatment of Thyroid Diseases"; and Dr. George T. Harrell, Jr., F.A.C.P., Gainesville, Fla., who participated in a clinical pathological conference.

Dr. Edgar V. Allen, F.A.C.P., Rochester, Minn., spoke on the "Treatment of Essential Hypertension" at the 65th Annual Convention of the Washington State Medical Association in Spokane, Sept. 19–22.

Drs. Willis M. Fowler, F.A.C.P., Iowa City, College Governor for Iowa, and Charley J. Smyth, F.A.C.P., Denver, Colo., were two of the guest speakers at the 76th Annual Meeting of the Montana Medical Association, held in Butte, Sept 16–19. Dr. Fowler's papers were entitled "The Treatment of Leukemia and Related Diseases" and "Medical Treatment of Thyroid Disease and the Use of Radioactive Iodine." Dr. Smyth discussed "Recent Developments in Gout and Its Therapy."

Among the out-of-state speakers at the 104th Annual Session of the Medical Society of the State of Pennsylvania, held in Philadelphia, Oct. 17–22, were Drs. Cornelius P. Rhoads, F.A.C.P., New York City, and Harold Feil, F.A.C.P., Cleveland. Dr. Rhoads' subject was "Rational Cancer Chemotherapy." Dr. Feil discussed "Clinical Aspects" in a Symposium on Coronary Heart Disease, and also participated in a panel discussion on this subject.

Dr. Stewart G. Wolf, Jr., F.A.C.P., Oklahoma City, spoke on "Visceral Pain Mechanism. Evaluation of Treatment in Disease" at the 84th Annual Session of the Colorado State Medical Society at Colorado Springs, Sept. 21–24.

Dr. J. Burns Amberson, F.A.C.P., New York City, delivered the Second Harlow Brooks Lecture and received a medal in memory of the late Dr. Brooks, F.A.C.P., at the 27th Annual Graduate Fortnight of the New York Academy of Medicine, which was held Oct. 18–29 in New York City. The title of Dr. Amberson's lecture was

"Current Methods in the Treatment of Tuberculosis." Out-of-state speakers who contributed to the scientific sessions were Dr. C. H. Rammelkamp, Jr., F.A.C.P., Cleveland, "The Epidemiology of Hemolytic Streptococcal Infections"; Dr. Louis Weinstein, F.A.C.P., Boston, "The Complications of Antibiotic Therapy"; and Dr. J. Vernon Knight (Associate), Nashville, Tenn., "Staphylococcus Infections."

Four members of the College were among the guests of the Kansas City Southwest Clinical Society at its 32nd Annual Conference, held in Kansas City, Mo., Oct. 4–7. Dr. Lucian A. Smith, F.A.C.P., Rochester, Minn., spoke on "Pain Patterns in the Diagnosis of Chronic and Recurrent Diseases of the Abdomen" and participated in a clinico-pathologic conference and a panel on "The Acute Abdomen." Dr. William A. Sodeman, F.A.C.P., Columbia, Mo., presented a paper on "Glomerulosclerosis" and participated in a seminar on "Blood Dyscrasias." Dr. Tom D. Spies, F.A.C.P., Birmingham, Ala., discussed "Vitamins and Other Nutrients in the Day-to-Day Practice of Medicine." Dr. Travis W. Winsor, F.A.C.P., Los Angeles, spoke on "The Management of the Cardiac Arrhythmias," participated in a conference on "Peripheral Vascular Disease," and conducted a Peripheral Arterial Diseases Clinic on color television with Dr. F. Stanley Morest, F.A.C.P., Kansas City. Dr. Sodeman and Dr. Spies also took part in a panel discussion on "The Rational Use of Antibiotics."

Dr. George E. Burch, Jr., F.A.C.P., New Orleans, was one of the guest speakers at the annual meeting of the Georgia Heart Association in Savannah, Sept. 24–25. His topic was "An Evaluation of the Vectorcardiogram for Clinical Use. Clinical Aspects of Venous Pressure Measurements."

Drs. J. Minott Stickney, F.A.C.P., and Talbert Cooper, F.A.C.P., both of Rochester, Minn., presented a Symposium on Anemia at the annual meeting of the Iowa Academy of General Practice in Des Moines, Sept. 22–23. Dr. Stickney also discussed "Treatment of Leukemia," and Dr. Cooper, "Treatment of Hodgkin's Disease and Lymphoblastoma." Dr. Francis D. Murphy, F.A.C.P., Milwaukee, delivered the Dr. Ernest E. Shaw Lecture, "Acute Renal Insufficiency, Including Acute Toxic Nephrosis" and spoke on "Management of Hypertension with Special Reference to Newer Methods of Treatment."

Discussing "Treatment of Hyperthyroidism," Dr. E. Perry McCullagh, F.A.C.P., Cleveland, was among the out-of-state speakers at the annual meeting of the Kentucky State Medical Association in Louisville, Sept. 21–23.

"Male Hypogonadism" was the topic of the address delivered by Dr. Harry F. Klinefelter, Jr., F.A.C.P., Baltimore, at a regional meeting of the West Virginia Academy of General Practice in Clarksburg, Sept. 19.

Dr. Ovid O. Meyer, F.A.C.P., Madison, Wis., spoke on "Some Aspects of the Anemias" at a meeting of the Hartford (Conn.) Medical Society on Oct. 4.

Dr. G. Watson James, III (Associate), Richmond, Va., presented a paper on "Stercobilin and Hematopoiesis" as part of a Symposium on the Nutritional Aspects of Blood Formation, which was held at the University of Cincinnati, Oct. 22, and was sponsored by the National Vitamin Foundation.

Dr. Charles A. Doan, F.A.C.P., Columbus, College Governor for Ohio, contributed to the postgraduate radio program series "For Doctors Only," broadcast by station WNYC, New York City. His subjects on Sept. 16 and Oct. 7 were, respectively, "White Blood Cells in Health and Disease" and "The Action of Drugs and Toxic Agents on the Blood Picture."

Dr. Irving S. Wright, F.A.C.P., College Governor for Eastern New York, and Dr. William T. Foley, F.A.C.P., New York City, attended the First World Conference on Thrombo-embolism, held in Basle, Switzerland, July 20–24, and presented several papers on problems of thrombo-embolism and studies of new anticoagulants. There were more than 800 physicians and chemists from 41 countries present. An International Committee for the Standardization of Nomenclature of Blood Clotting Factors was appointed, and Dr. Wright was made Chairman of the Committee.

Dr. Carll S. Mundy, F.A.C.P., Toledo, Ohio, discussed "Roads to Rural Health" during the Seventh Annual Rural Health Conference, sponsored by the West Virginia State Medical Association and held at Jackson's Mill, Sept. 2. Dr. Mundy is Vice Chairman of the Council on Rural Health of the American Medical Association.

In addition to Dr. E. Cowles Andrus, F.A.C.P., Baltimore, as reported in a previous issue of this journal, Dr. A. Carlton Ernstene, F.A.C.P., Cleveland, was also one of the principal speakers during the annual meeting of the West Virginia Heart Association, held in Huntington, Nov. 5.

Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, delivered the opening lecture in a series of weekly talks on cancer presented by Northwestern University Medical School, Chicago, Oct. 6–Nov. 17. Dr. Reimann's subject was "Differentiating and Chromosomal Influences in the Growth of Cancers."

Seven members of the College were among the guest speakers at the 89th Annual Session of the Michigan State Medical Society, which convened in Detroit, Sept. 29–Oct. 1. From Chicago, Drs. Richard B. Capps, F.A.C.P., Francis E. Senear, F.A.C.P., and I. Davidsohn, F.A.C.P., spoke, respectively, on "Acute Viral Hepatitis: Epidemiology, Diagnosis and Treatment," "Advances in Dermatologic Therapy," and "Hodgkin's Disease." Dr. Chris J. D. Zarafonetis, F.A.C.P., Philadelphia, discussed "Para-Aminobenzoic Acid in the Treatment of Scleroderma and Other Disorders Associated with Excessive Fibrosis." The respective subjects of Drs. Paul A. O'Leary, F.A.C.P., Rochester, Minn., and W. Paul Holbrook, F.A.C.P., Tucson, Ariz., were "Nodular and Ulcerative Lesions of the Lower Extremities" and "Treatment of Rheumatoid Arthritis." Dr. Robert L. Levy, F.A.C.P., New York City, discussed "Restrictions for Cardiacs—Necessary and Needless."

Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Regent, was the after-dinner speaker at an Institute on Gerontology and the General Practitioner, held at the State University of Iowa, Iowa City, Oct. 1. The title of his address was "Gerontology—Its Relation to Medicine and Society."

Speaking on "Arthritis," Dr. Russell L. Cecil, F.A.C.P., New York City, addressed the annual scientific assembly of the South Carolina Academy of General Practice, which was held in Columbia, Sept. 28–29.

Dr. Herman J. Moersch, F.A.C.P., Rochester, Minn., spoke on "Differential Diagnosis of Carcinoma of the Lung" at the annual meeting of the Wisconsin Chapter of the American College of Chest Physicians in Milwaukee, Oct. 3.

Dr. Gilbert H. Marquardt, F.A.C.P., Chicago, was the guest of the Director's Committee on Religious Activity of the Methodist Hospital in Lubbock, Tex., Oct. 7–8, when a lecture-clinic for physicians and ministers, "Serving the Suffering," was presented. With Russell L. Dicks, D.D., Dr. Marquardt discussed various phases of the inter-relationship between the physician and the minister and the rôles each plays in assisting the sick and the dying.

Col. Santino J. Lerro, (MC), USA, (Associate), has been assigned as Assistant Chief Medical Consultant, Professional Division, Office of the Surgeon General, Department of the Army, Washington, D. C.

Dr. Alvin J. Cummins (Associate), formerly of Philadelphia, has recently joined the staff of the University of Tennessee College of Medicine, Memphis, as Assistant Professor of Medicine. In addition, Dr. Cummins has been appointed to the staff of the John Gaston Hospital, where he will develop a postgraduate training program for research fellows and residents.

Dr. Robert E. Stone, F.A.C.P., Birmingham, Ala., has recently been promoted to Professor of Nutrition and Metabolism of Northwestern University Medical School, Evanston, Ill. Dr. Stone is Associate Scientific Director of Northwestern's Nutrition Clinic at Jefferson-Hillman Hospital, Birmingham.

Rear Adm. Joel J. White, (MC), USN, Retired, F.A.C.P., as of April 28, 1954, became Medical Director-Administrator of Duval Medical Center, Jacksonville, Fla. Adm. White was formerly Medical Director of St. Mary's Memorial Hospital, Knoxville, Tenn.

Dr. Michael B. Shimkin, F.A.C.P., formerly of San Francisco, where he was Chief of the U. S. Public Health Service Laboratory of Oncology, has recently become Chief of the Biometry and Epidemiology Branch of the National Cancer Institute.

Dr. Snowden C. Hall, Jr., F.A.C.P., Danville, has recently been appointed a member of the Virginia State Board of Medical Examiners.

Dr. George Bachmann, F.A.C.P., Atlanta, was appointed by Dr. Walter L. Bierring, M.A.C.P., Des Moines, Iowa, President of Alpha Omega Alpha Honor Medical Society, to represent the Society at the Centennial Celebration of Emory University School of Medicine, Oct. 4–5. Dr. Bachmann is Professor Emeritus of Physiology at Emory.

Dr. Wilmar M. Allen, F.A.C.P., Hartford, Conn., is serving for nine months as Hospital Consultant to Belgium. Dr. Allen, who assumed his new post last month under the Fulbright Foundation, was formerly Director of the Hartford Hospital and is now its Consultant.

Dr. James L. McCartney, F.A.C.P., of Garden City, N. Y., has been invited to speak, under the auspices of the World Medical Association, to the medical societies at Havana, Cuba; Yokohama and Kobe, Japan; Manila, P. I.; Colombo, Ceylon; Cochin and Bombay, India; Karachi, Pakistan; Naples and Genoa, Italy. His subject will be "The Treatment of the Involutional and Senile Psychoses."

Dr. William C. Menninger, F.A.C.P., Topeka, College Governor for Kansas, and Dr. Howard A. Rusk, F.A.C.P., New York City, were among the leaders in the rehabilitation, health, and welfare fields who participated in the 31st Convention of the National Society for Crippled Children and Adults, held earlier this month in Boston, Mass.

Drs. R. Wayne Rundles, F.A.C.P., and Samuel P. Martin (Associate), Durham, N. C., addressed the International Congress of Hematology in Paris, France, Sept. 10. Dr. Rundles discussed "Abnormal Proteins in Malignant Blood Disease" and Dr. Martin spoke on "Leukocyte Metabolism."

Dr. Rundles also visited the Royal Cancer Society and blood laboratories in London and Paris, as well as protein laboratories in Sweden before his return later in the month. Dr. Martin discussed "Metabolic Response to Infection" in a symposium sponsored by the Ciba Foundation in London, Oct. 8.

OBITUARIES

DR. MAHLON ASHFORD

Dr. Mahlon Ashford, a Fellow of the American College of Physicians since 1938, died in Washington, D. C., on June 5, 1954. He died in his sleep and the exact cause of death was not determined.

Dr. Ashford was born in Washington, D. C., on March 24, 1881. He attended Columbia University from 1899–1901, and received his M.D. from Georgetown University School of Medicine in 1904. Following this, he served as a Resident at the Georgetown University Hospital during 1904–05 and at the Columbia Hospital for Women and Lying-In Asylum from 1905–07. In the years 1904–07, he also served as an Instructor in Physics in the Georgetown University School of Medicine.

Dr. Ashford pursued his postgraduate studies at the United States Army Medical School during 1907–08, where he was an honor graduate and medalist, and he entered the United States Army Medical Corps in 1908. He served as an Associate in Medicine in the United States Army Hospital in Washington, D. C., in 1908–09. He was Chief of Medical Service of the United States Army Brigade Hospital in Manila from 1909–11. He was in charge of the Hospital and Medical Service of the Hospital Coast Defense of the Potomac in Washington during 1912–14. Dr. Ashford was Executive Officer of the Walter Reed Army Hospital, 1919–20; Chief of the Personnel Division, Office of the Surgeon General, 1920–24; Medical Inspector, Third Corps Area, 1925–29; Department Medical Inspector and Acting Department Surgeon of the Hawaiian Department, 1929–31; Attending Surgeon, U. S. Army for New York City, 1931–35, and Department Surgeon of the U. S. Army in Panama, 1935–36. Retiring from the Army as a Colonel in 1936, he thereafter became Executive Secretary of the Committee on Medical Education, and Editor of the Bulletin of the New York Academy of Medicine from 1937 until his retirement in July, 1951.

Dr. Ashford made many conspicuous contributions to the science of medicine during his years in the United States Army Medical Corps. He was the author of numerous monographs, including Wellcome Prize Essays. He was a Fellow of the American College of Surgeons and a member of the American Medical Association and of the New York Academy of Medicine. During the latter years of his active life, as Executive Secretary for the Committee on Medical Education, Dr. Ashford provided significant leadership in the development of postgraduate medical education provided by the New York Academy of Medicine.

Dr. Ashford's kind and gentle spirit endeared him to innumerable friends and associates, both in the military and civilian medical profession. It is with deepest personal regret that his passing is recorded.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. JOHN M. BELL

Dr. John Malseed Bell, F.A.C.P., of St. Joseph, Mo., a charter member of the American College of Physicians, died on May 26, 1954. Born in Philadelphia, Pa., on Jan. 8, 1865, he had remained active and in good health in spite of his 89 years until six days before his death, when he suffered a cerebro-vascular accident.

After his father's death, Dr. Bell was enrolled in Girard College, a preparatory school for boys at Philadelphia. After graduation he attended the University of Pennsylvania in 1885–86, moved to Nebraska where he worked for several years as a pharmacist, and then finished his medical education at the old Northwestern Medical College in St. Joseph, Mo. Following his graduation in 1892, he served successively until 1913 as Professor of Chemistry at the Northwestern, Central, and Ensworth

Medical Colleges. In the last institution, he also held the title of Professor of Stomach and Intestinal Diseases. Dr. Bell was for many years a staff member at the Missouri Methodist and St. Joseph's Hospitals. He was President of the St. Joseph Board of Health, 1920–22; Treasurer of the Buchanan County Medical Society, 1910–35; First Vice President of the Missouri State Medical Association, 1909–10; President of the St. Joseph Medical Society in 1902, and of the Missouri Valley Medical Society, 1911–12. For many years he served as Associate Editor of the *Medical Herald*. Dr. Bell closed his office about six years ago but continued to attend a few of his old patients.

Dr. Bell loved people, had many friends, and worked among them as a citizen as well as a physician. For one period of six years, he served as a member of the school board. He had been an elder in his church for 24 years and had taught a men's Bible class for 38 years. Following the death of his wife, Harriett Braddock Bell, in 1942, he continued to live in the family home. He is survived by a daughter, Mrs. Harriett Elliff, and a son, Dr. Robert M. Bell, who is a member of the faculty at the Washington University School of Medicine.

CARL V. MOORE, M.D., F.A.C.P.,
Governor for Missouri

DR. JAMES W. CALLAWAY

Dr. James Willis Callaway, F.A.C.P., of La Jolla, Calif., died June 25, 1954, of adenocarcinoma of the pancreas.

Dr. Callaway was born in Temple, Tex., on Nov. 7, 1907, and graduated from Southern Methodist University in 1927 with the degree of Bachelor of Arts. He then attended Northwestern University Medical School, where he received his M.S. degree in 1931 and his M.D. degree in 1933.

After an internship and residency in Chicago's St. Luke's and Municipal Contagious Disease Hospitals, he joined the Scripps Metabolic Clinic in 1934 as an Associate Physician, a position which he held at the time of his death. He was also a member of the Active Staff of Scripps Memorial Hospital and President of the Staff in 1947. During World War II, Dr. Callaway served with the U. S. Army Medical Corps for more than five years and was Chief of Medical Service at various general hospitals on the West Coast. He was separated Feb. 27, 1946, with the rank of Lieutenant Colonel. He held memberships in the San Diego County Medical Society and the California Medical, American Medical, American Diabetes, and American Heart Associations. A Diplomate of the American Board of Internal Medicine, Dr. Callaway had been a Fellow of the American College of Physicians since 1948.

Dr. Callaway's very personalized approach to a patient's problem was by application of a what-when-where-why principle. Nothing was overlooked or left to chance. If some obscurity remained, he admitted his lack of knowledge. False deductions or conclusions were never allowed to comfort his ego or confuse his judgment. His great success as internist and skillful diagnostician was therefore firmly established. In treatment he was a gentle, therapeutic nihilist.

Dr. Callaway's outlook on life was practical and cheerful. Through many months of cruel illness, his closest associates never heard a complaining word, never any angry outburst against the unkind fate that cut him down in the prime of life. His courage was superlative.

Greatly missed by his professional colleagues, Dr. Callaway's death is even more keenly felt by the host of patients who daily benefited through his mildly humorous, although firm, application of a great medical knowledge and judgment.

FRANCIS M. SMITH, M.D.

COL. VIRGIL HEATH CORNELL

Col. Virgil Heath Cornell, (MC), USA, Retired, died suddenly on June 3, 1954, of acute coronary occlusion in Washington, D. C.

Col. Cornell was born in Brooklyn, N. Y., Nov. 29, 1890, and graduated from the Long Island College Hospital in 1913. Commissioned a First Lieutenant in the Army Medical Reserve Corps on Sept. 7, 1917, he first attended the Medical Officers' Training Corps at Camp Greenleaf, Oglethorpe, Ga., and later graduated with honors from the Army Medical School in Washington, D. C., and the Medical Field Service School, Carlisle Barracks, Pa. Until his retirement due to physical disability on Aug. 18, 1950, Col. Cornell experienced almost 33 years of continuous Army service. He was promoted to Captain in 1920, Major in 1929, Lieutenant Colonel in 1937, and Colonel in 1943. During his long and distinguished career as a medical officer, he served at the New York Port of Embarkation, Camp Mills, Fort Thomas, Fort Banks, The Canal Zone, Presidio of San Francisco, New York City, Puerto Rico, Fort McPherson, in the Mediterranean Theater during World War II, and several tours of duty in Washington, D. C., as Curator of the Army Medical Museum and Laboratory Officer at the Army Medical Center. After his retirement, Col. Cornell became Professorial Lecturer in Pathology at George Washington University School of Medicine and Pathologist to the Washington Sanitarium and Hospital, which positions he held at the time of his death.

Col. Cornell was awarded the Sternberg Medal in 1921 and was the author of numerous medical articles. Further recognition of his stature in medicine was accorded him in 1943 when Harvard University bestowed on him the degree of Doctor of Public Health. His Army decorations included the Legion of Merit, American Defense Medal, American Campaign Medal, World War I and World War II Victory Medals, European-African-Middle East Campaign Medal with Silver Star, Bronze Arrowhead, and one Bronze Service Star.

Col. Cornell had been President of the Medical Association of the Isthmian Canal Zone in 1926 and of the Pasteur Society of Central California during 1929–30. He was also Vice President of the San Francisco Pathological Society during 1930–31. In addition, he was a member of the American Public Health Association, the American Association of Pathologists and Bacteriologists, International Association of Medical Museums, American Medical Association, American Society of Tropical Medicine, and the Association of Military Surgeons of the United States. A Diplomate of the American Board of Pathology and of the American Board of Preventive Medicine and Public Health, Col. Cornell was elected to Fellowship in the American College of Physicians in 1932.

DR. RALPH M. FELLOWS

Dr. Ralph Manos Fellows, F.A.C.P., died on June 27, 1954, after a year's illness due to hypertensive and arteriosclerotic heart disease.

He was born in Salisbury, Mo., on Aug. 28, 1894, and received his A.B. degree from the University of Missouri in 1917 and his M.D. degree from New York University and Bellevue Hospital Medical College in 1922. He was Acting Assistant Surgeon to the U. S. Public Health Service in Galveston, Tex., 1932–33; Psychiatrist at the Menninger Sanitarium, 1933–36; Superintendent of the Osawatomie State Hospital, Osawatomie, Kans., 1936–40; Assistant Medical Director of the Milwaukee County Hospital for Mental Diseases, 1940–43. From 1944–46 he served as Psychiatrist at the United States Naval Hospital, San Diego, Calif., and as Psychiatric Consultant to the United States Naval Retiring Board, holding the rank of Lieutenant Commander. He served as Clinical Director of the Veterans Administration Hospital at Palo Alto, Calif., from 1946–47, at which time he was appointed Medical Director of the Milwaukee County Asylum, a position which he held until his death.

He was a Fellow of the American College of Physicians from 1936 and a member of the American Psychiatric Association, Central Neuropsychiatric Society and American Medical Association. A former President of the Chariton County Medical Society in Missouri, Dr. Fellows was a Diplomate of the American Board of Psychiatry and Neurology.

Dr. Fellows was highly respected by his colleagues and patients alike, not only for his clinical but for his administrative ability as well. He contributed generously of his time and energy to the Society for Mental Health and in 1953 was the recipient of an award for "Notable and outstanding contributions to the field of Mental Health."

F. W. MADISON, M.D., F.A.C.P.,
Governor for Wisconsin

DR. ROY HERBERT HOLMES

Dr. Roy Herbert Holmes, F.A.C.P., entered the practice of medicine in Muskegon, Mich., in 1923, where he died on May 4, 1954, the cause of death being coronary occlusion.

He was born Jan. 22, 1896, in Grand Rapids and attended the University of Michigan and Kalamazoo College, receiving his M.D. degree from the University of Michigan Homeopathic Medical School in 1922. Dr. Holmes interned at the Massachusetts Homeopathic Hospital in Boston from 1922 through 1923. He became Consultant in Medicine at the Hackley Hospital in Muskegon in 1925 and was Associate Head of the Pediatric Service from 1927 through 1931. He was Head of the Pediatric Service from 1932 until 1936 and was Chief Consultant in Dermatology from 1937 until 1954. He was also Consultant in Medicine from 1930 through 1936 and Consultant in Dermatology and Syphilology from 1937 until 1954 at the Mercy Hospital. During World War II he served as a member of the Regional Medical Appeal Board and as Major, (MC), AUS, from August, 1942, until May, 1945.

Dr. Holmes was a former Editor of *The Journal of the Michigan State Medical Society*. He was a member of the Muskegon County and Michigan State Medical Societies, the American Medical Association, the Detroit Dermatological Society, the American Society of Industrial Physicians and Surgeons, the American Academy of Dermatology and Syphilology, the Society for Investigative Dermatology, and Theta Kappa Psi. He became a Fellow of the American College of Physicians in 1936.

About 1930, Dr. Holmes became interested in certain dermatological problems in industry. This interest led him to a postgraduate study at the New York Skin and Cancer Hospital during 1936 and 1937. From that time on he limited his practice to dermatology. He devoted a great deal of energy to the activities of the Muskegon County Medical Society. He developed the first bulletin for that organization and remained Editor of it until entering the Armed Forces in 1942. He served as President of the County Medical Society for the year 1941 and was very active on its Public Relations Committee for several terms. At the time of his death he was Medical Legal Advisor to the Society.

In all of his work in the interests of the County Medical Society, he was ever conscious of the pressure for federalization of medicine and contributed much to the successful fight against this evil influence in the state during those depression years when this movement was so strong.

H. M. POLLARD, M.D., F.A.C.P.,
Governor for Michigan

DR. WILFRED D. LANGLEY, SR.

Wilfred Derwood Langley, Sr., M.D., F.A.C.P., died March 18, 1954, at the Guthrie Clinic-Robert Packer Hospital, Sayre, Pa., where he had been a patient since Feb. 26 when stricken with a cerebral hemorrhage.

Born in Glen Lyon, Pa., Sept. 17, 1903, Dr. Langley was graduated from the University of Pennsylvania in 1928, and four years later received his M.D. from the University of Pennsylvania School of Medicine. He had been associated with the Robert Packer Hospital since 1932, when he commenced his internship, and at the time of his death, was an Associate in Internal Medicine, a position he had held since 1936. In 1953 Dr. Langley became Clinical Professor of Medicine (Affiliate) at Hahnemann Medical College and Hospital of Philadelphia.

A member of the Medical Society of the State of Pennsylvania and the American Medical Association, Dr. Langley served as President of the Bradford County Medical Society in 1942. He was a member of the Central Pennsylvania Allergy Society and a Diplomate of the American Board of Internal Medicine. He was elected to Fellowship in the American College of Physicians in 1939. Active in community life, Dr. Langley was President of the Sayre School Board and Senior Warden at his church.

DR. JAMES C. McADAMS

On May 9, 1954, Dr. James Carlin McAdams, one of the leading internists of Fall River, Mass., and a Fellow of the American College of Physicians since 1939, died.

Dr. McAdams was a graduate of DePauw University and received his medical degree from the University of Pennsylvania School of Medicine in 1926. After interning at the Hospital of the University of Pennsylvania, in 1928 he took up his residence in Fall River and during his 26 years of practice in that city became recognized as one of its leading clinicians.

Since 1928 he had been a physician at the Truesdale Hospital and since 1947 a member of its Board of Trustees. He was also Physician, and since 1945 Consulting Physician, to the Fall River General Hospital. He was active in local medical affairs, serving as President of of the Fall River Medical Society in 1939. He was a Diplomate of the American Board of Internal Medicine and of the National Board of Medical Examiners. In addition to membership in the Massachusetts Medical Society and the American Medical Association, he took an active part in the affairs of the New England and the American Heart Associations. He was a member of the Alpha Omega Alpha fraternity.

Dr. McAdams was a strong personality with a strong character, and considerations of personal gain never influenced his expression of his sincere convictions. Strict with his patients for their own welfare, his relations with them were kindly and frank and commanded the respect of all of his patients and the love of the majority of them.

His death is a real loss to the medical profession of Fall River and to the many individuals and organizations for whose advancement and welfare he gave generously of his time and efforts.

RICHARD P. STETSON, M.D., F.A.C.P.,
Governor for Massachusetts

DR. L. J. MOORMAN

Dr. Lewis Jefferson Moorman, aged 79, Fellow of the American College of Physicians since 1920, Diplomate of the American Board of Internal Medicine, nationally known authority on tuberculosis, pioneer physician of Oklahoma and author of *Pioneer Doctor*, died in Oklahoma City, Aug. 2, 1954.

Dr. Moorman was a native of Kentucky, received his medical degree at the University of Louisville School of Medicine in 1901 and came to Oklahoma soon thereafter. He practiced at Chickasha for a short time and then went to the small

frontier village of Jet, where he did frontier practice until 1907 when he moved to Okahoma City. He became interested in tuberculosis and in 1914 opened the first private sanatorium for the treatment of tuberculosis in Oklahoma, which he operated until 1947.

During these years Dr. Moorman acquired national prominence in his chosen field and was the recipient of many honors. Besides being elected President of his county and state medical societies, he also headed at various times the American Clinical and Climatological Association, the Southern Tuberculosis Conference, the National Tuberculosis Association, the American Trudeau Society, the Southern Medical Association, the American Medical Writers Association, and others. In 1949 he was a guest speaker at the London Osler Club and at the British National Association for the Prevention of Tuberculosis, and in 1952 he addressed the World Medical Association meeting in Athens. He was the author of *Tuberculosis and Genius* as well as *Pioneer Doctor.*

For the last fifteen years Dr. Moorman had been Secretary-Editor of the Oklahoma State Medical Association and Journal. He was a past Dean of the University of Oklahoma School of Medicine, and at the time of his death was Emeritus Professor of Medicine as well as an honorary member of the staff of St. Anthony Hospital. In 1948 he was chosen as a member of a committee of five to study health conditions of the Navajo Indians.

This community, the Oklahoma State Medical Association, and American Medicine have sustained a great loss in the passing of Dr. Moorman.

WANN LANGSTON, M.D., F.A.C.P.,
Governor for Oklahoma

DR. SAM I. MILLER

Dr. Samuel Irving Miller, F.A.C.P., of Houston, Tex., died on July 11, 1954, in a local hospital.

A native of Texas, Dr. Miller was born in Galveston on Dec. 14, 1912. He graduated from the Rice Institute, Houston, in 1933, and received his M.D. degree from the University of Texas School of Medicine in 1938. After an internship at the Michael Reese Hospital in Chicago, he served as an assistant resident in medicine during 1940–41 at the Albert Merritt Billings Hospital in Chicago; his residency was at the Joseph H. Pratt Diagnostic Hospital in Boston in 1941–42.

Dr. Miller joined the faculty of Baylor University College of Medicine in Houston in 1947, and since 1951 he had been Assistant Professor of Clinical Medicine, both at Baylor University and at the University of Texas Postgraduate School of Medicine.

For some years Dr. Miller was connected with the staff of the Veterans Administration Hospital, the Jefferson Davis Hospital and the Methodist Hospital, all of Houston. He served in the Army of the United States from 1942–46 and was separated with rank of Major.

Dr. Miller had been a member of the Texas and American Medical Associations continuously since 1947. He was certified by the American Board of Internal Medicine and was elected a Fellow of the American College of Physicians in 1952. Dr. Miller had been a member of the American Heart Association, the Houston Society of Internal Medicine, and Alpha Omega Alpha fraternity.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. BRYAN M. RILEY

Bryan Michael Riley, M.D., F.A.C.P., was born in Dawson, Nebr., on Feb. 7, 1874, and passed away on April 19, 1954, the cause of death being intestinal obstruction and uremia.

Dr. Riley was granted the degree of Bachelor of Arts in 1896 from St. Mary's College and the degree of Doctor of Medicine in 1900 from Creighton University School of Medicine. He joined the medical staff of Creighton Memorial St. Joseph's Hospital in 1908, later becoming Professor of Clinical Medicine and Chief of Staff. He had been Attending Physician at St. Catherine's Hospital since 1932 and Consulting Physician at the Douglas County Hospital. He served on the teaching staff of Creighton University School of Medicine as Assistant in Medicine, Associate in Medicine, Professor of Medicine, and in 1933 was appointed Dean. In 1939 he retired from the Deanship and was made Emeritus Professor of Medicine. He continued in the private practice of medicine until the time of his death.

Dr. Riley was active in medical organization work, serving as President of the Omaha-Douglas County Medical Society in 1932–33; he was a Charter Member of the Omaha Mid-West Clinical Society and President in 1938, a member of the Nebraska State Medical Association and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1920. His fraternities were Phi Rho Sigma and Pi Upsilon.

Dr. Riley was a true physician. He gave much of himself to teaching, medical administration, organizational work and to private practice. The College and his local confreres have lost, in Dr. Riley's passing, a valuable friend and ardent worker, dedicated to the advancement of the practice of medicine and the education of medical students as well as graduates.

JOSEPH D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. N. B. VAN ETTEN

Dr. Nathan Bristol Van Etten, a Fellow of the American College of Physicians, died from bronchopneumonia on July 23, 1954, at St. Barnabas Hospital for Chronic Diseases in the Bronx.

He was born in Waverly, N. Y., on June 22, 1866, and was a founder of Phi Alpha Sigma Medical Fraternity in 1888. He graduated from Bellevue Hospital Medical College in 1890 with the degree of M.D. He was formerly Medical Director and Visiting Physician of the Morrisania City Hospital; Visiting Physician and Chairman of the Medical Board of the Union Hospital; Consulting Physician for the Home for Incurables, Bronx Eye and Ear Infirmary, Seton Hospital, and for St. Barnabas Hospital for Chronic Diseases. He served as President of the Bronx County Medical Society in 1914, the New York Society of Medical Jurisprudence in 1921, and of the Medical Association of the Greater City of New York in 1923.

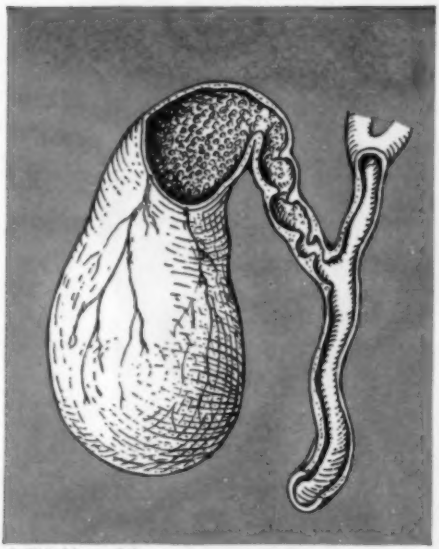
Dr. Van Etten was Editor of the *New York State Journal of Medicine* from 1920 to 1925. He became President of the New York State Medical Society in 1925 and was elected to the high office of President of the American Medical Association from 1940 to 1941. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1933. He served as Chairman of the Board of Directors of the United Medical Service from 1944 to 1948.

Dr. Van Etten was widely known for his interest in the welfare of his fellow physicians. He consistently held positions of responsibility and trust, as indicated by the list of important societies in which he held the office of President. He was truly an elder statesman of medicine and was beloved by a host of physicians and patients. His passing was noted with deep sorrow.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

By increasing bile secretion with Ketochol® and controlling sphincter of Oddi spasticity with Pavatrine®, a free flow of bile is instituted with resultant symptomatic improvement.

Conservative, Effective Medical Management of Chronic Gallbladder Disease



Gallbladder and ducts.

The ketocholanic acids in Ketochol stimulate the flow of hepatic bile and flush the bile ducts. Antispasmodic medication, as provided in Pavatrine, diminishes gastrointestinal irritability and, by relaxing the sphincter of Oddi, effectively reduces symptoms of colic. This therapeutic program offers rational, conservative therapy in gallbladder dysfunction.

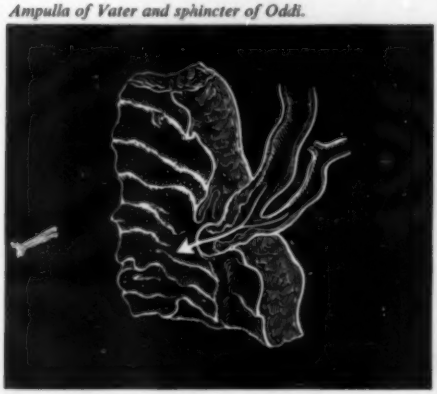
That the four bile acids present in Ketochol relieve biliary stasis is even more definitely proved by their use in the diagnosis of nonvisualized gallbladders. After the administration of Ketochol, repeat cholecystograms permitted[1] correct diagnoses.

In conjunction with the foregoing medication, proper diet, adjusted intake of milk and cream and mental relaxation are important.

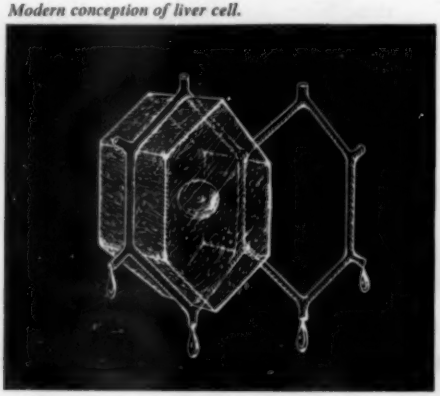
The average dose of Ketochol is one tablet three times daily with or following meals. The average dose of Pavatrine or Pavatrine with Phenobarbital is one or two tablets three or four times daily as needed. G. D. Searle & Co., Research in the Service of Medicine.

1. Berg, A. M., and Hamilton, J. E.: A Method to Improve Roentgen Diagnosis of Biliary Diseases with Bile Acids, Surgery *32*:948 (Dec.) 1952.

Ampulla of Vater and sphincter of Oddi.



Modern conception of liver cell.



is this your dieting patient?

Obocell successfully depresses appetite and suppresses "bulk hunger" *at* meals and *between* meals. The two ingredients of Obocell—Nicel* and d-Amphetamine—work together. Nicel controls release of amphetamine into the blood stream. This serves to provide both quick and sustained control of appetite. In addition, Nicel, an efficient water-binding agent, provides the necessary bulk to create a sense of fullness, suppressing "bulk hunger."

Obocell stills the urge of your patients to snack and violate their diets. It's economical for them, too.

Each Obocell tablet supplies:
d-Amphetamine Phosphate (dibasic)..5 mg.
Nicel*.....150 mg.
*Irwin-Neisler's brand of specially prepared high viscosity methylcellulose.
Bottles of 100, 500, 1000.

Obocell® DOUBLES THE POWER TO RESIST FOOD

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

Combination tranquilizer-antihypertensive
especially for
moderate and severe
essential hypertension . . .
T.M.
Serpasil-Apresoline®
hydrochloride
(RESERPINE AND HYDRALAZINE HYDROCHLORIDE CIBA)
Combined in a Single Tablet
• The tranquilizing, bradycrotic and mild antihypertensive effects of Serpasil, a pure crystalline alkaloid of rauwolfia root.
• The more marked antihypertensive effect of Apresoline and its capacity to increase renal plasma flow.
Each tablet (scored) contains 0.2 mg. of Serpasil and 50 mg. of Apresoline hydrochloride.
CIBA
SUMMIT, N. J.

in the treatment of Hypertension

Prolonged effect of mannitol hexanitrate

lowers pressure for 4 to 6 hours

New and Nonofficial Remedies, A.M.A. Council on Pharmacy and Chemistry, J. B. Lippincott, p. 242, 1953.

Marked diuretic action of theophylline

facilitates sodium excretion

Med. Times *81*:266 (Apr.) 1953.

Phenobarbital for relaxation without hypnosis

most useful for promoting daytime relaxation

J.A.M.A. *147*:1311 (Dec.) 1951.

Ascorbic acid + rutin for capillary protection

help to maintain capillary integrity

Delaware State M. J. *22*:283 (Oct.) 1950.

Semhyten®

BRINGS THE PRESSURE DOWN SLOWLY SAFELY

Complete Medication for the Hypertensive

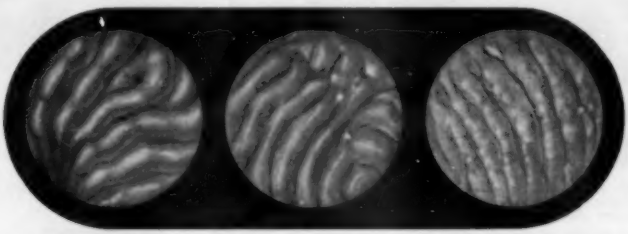
Each Semhyten Capsule contains:	Phenobarbital..¼ gr. (15 mg.)
Mannitol Hexanitrate....½ gr. (30 mg.)	Rutin .....10 mg.
Theophylline .....1½ gr. (0.1 Gm.)	Ascorbic Acid .....15 mg.

Supplied: In bottles of 100, 500 and 1000 pink-top capsules.

The S. E. MASSENGILL Company • Bristol, Tennessee

Please Mention this Journal when writing to Advertisers

"... the gastric secretion is the immediate agent of mucosal tissue digestion.... Opposed to this stands the defensive factor ... the two-component mucous barrier"[1] [*the protecting layer of mucus and the mucosal epithelium*].



Rotational gastroscopic views showing coating effect 1½ hours after administration of Amphojel.[3]

Causation — key to treatment in peptic ulcer

Through *topical* action alone, AMPHOJEL contends with the local causes of ulcer—aggressive acidity coupled with impairment of the wall defenses. Providing a dual approach, AMPHOJEL combines two aluminum hydroxide gels, one reactive, one demulcent. The reactive gel combats the attacking factor in ulcer by promptly buffering gastric acid. The demulcent gel promotes healing of the denuded mucosa by forming a viscous, protective coagulum.

AMPHOJEL—nonsystemic, nontoxic—provides time-proved *fundamental* therapy.

AMPHOJEL®

ALUMINUM HYDROXIDE GEL

Supplied: Liquid, bottles of 12 fluidounces
Tablets, 5 grain, boxes of 30, bottles of 100;
and 10 grain, boxes of 60 and 1000

References: 1. Hollander, F.: Arch. Int. Med. *93*:107 (Jan.) 1954
2. Deutsch, E.: Scientific Exhibit, Gastroscopy, Clinical Meeting A.M.A., St. Louis, December, 1953

Wyeth
Philadelphia 2, Pa.

Add Variety to

SODIUM RESTRICTED DIETS

CELLU SOYAMAISE—(Green Label) A salt-free, tangy mayonnaise type dressing. For delicious summer salads and hot vegetables. Sodium content averages 16.6 mg. in 100 grams.

CELLU CANNED TUNA—Packed in water without added salt or oil. Fine for salads and hot dishes. Sodium content averages 57 mg. per 100 grams of fish.

OTHER CELLU LOW SODIUM FOODS—Peanut Butter, Canned White Wheat Bread, Boned Chicken, Canned Salmon, Vegetables, Soups, Juices, Cake and many others.

FREE—Send for Cellu Catalog

CELLU SODIUM RESTRICTED *Dietary Foods*

CHICAGO DIETETIC SUPPLY HOUSE Inc.

BUY AND USE

CHRISTMAS SEALS

FIGHT

TUBERCULOSIS

DOCK*
BALLISTOGRAPH

**As described by William Dock, M.D., et al. Vol. 146, No. 14, Aug. 4, 1951, Jl. A. M. A. Ballistocardiography in Med. Prac.*

Compact design, engineered for accuracy, simplicity of use and clinical efficiency. No service required. Records on any make ECG. Simultaneous QRS reading.

$50.00 F.O.B. NEW YORK

With "leg block" carrying case—$12.50 extra

COUNTY SURGICAL CO., INC.
1237 Atlantic Ave., Brooklyn 16, N. Y.

To keep you posted, Doctor...

on up-to-date techniques for detecting and treating cancer, we have • • •

• • • in our professional film library, films on nearly 150 subjects covering cancer diagnosis, detection and treatment, available on loan • • •

• • • our monthly publication, "Cancer Current Literature," an index to articles on neoplastic diseases from American and foreign journals.

For information about these and other materials, write your state Division of the

American Cancer Society

WHY STABILITY IS IMPORTANT--

THE

● The improved stability of the Burdick EK-2 Direct-Recording Electrocardiograph makes it possible to switch from one standard lead to another instantaneously without any deviation of the base line.

The practical advantage of this feature is seen in the improved diagnostic accuracy of exercise tests and other technics where time is an important factor.

Burdick®

EK-2
DIRECT-RECORDING
ELECTROCARDIOGRAPH

ACCEPTED COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION AMERICAN MEDICAL ASSOCIATION

Ask your Burdick dealer for an office demonstration, or write us. No obligation.

UL

THE BURDICK CORPORATION
MILTON, WISCONSIN

is for
Reserpine
now combined
with
VERALBA*
for simpler,
safer, two-way
hypertension
therapy

VERALBA-R

PROTOVERATRINES A AND B WITH RESERPINE

In the treatment of mild, moderate, or malignant hypertension, combination of the protoveratrines with reserpine in VERALBA—R offers five outstanding clinical advantages:

1) Maintains normal or near-normal blood pressure indefinitely;
2) Combines additive vasodilation of two of the safest, most effective antihypertensive agents;
3) Tranquilizes the emotional patient;
4) Avoids unpredictable responses by the use of pure, crystalline alkaloids which are completely standardized by chemical assay;
5) Permits dosage schedule to be established easily, with continued and uniform responses to be expected thereafter.

SUPPLIED: Each VERALBA—R tablet contains 0.4 mg. of protoveratrine and 0.08 mg. of reserpine. *In bottles of 100 scored, uncoated pink tablets.*

PITMAN · MOORE COMPANY

DIVISION OF ALLIED LABORATORIES, INC.

INDIANAPOLIS, INDIANA

*TRADEMARK

Reducing patients can

EAT ALL THIS EVERY DAY

...AND LOSE WEIGHT SAFELY ON THE DIETENE® DIET

• Reducing patients eat much the same foods as other family members. No special foods, no special preparation. That's why the DIETENE 1000 Calorie Diet is easy to stick to!

• Between-meal DIETENE snacks (4 tablespoons DIETENE Reducing Supplement in 1 cup skim milk) maintain better nutritional balance than an ordinary diet! Hunger is *satisfied*, not suppressed.

• The DIETENE Diet is ideal for hypertension and cardiac cases. No drugs are involved!

DIETENE DIET IS BASED ON DIETENE...
the only Council-accepted Reducing Supplement

NOT ADVERTISED TO THE LAITY

• FREE continuing diet service saves time for you and your office help, yet each diet sheet looks individually typed!

DIETENE is available at all drug stores in plain or chocolate flavors. 1 lb. ($1.59) is full 8-day supply.

Mail Coupon for FREE 1-lb. can DIETENE Reducing Supplement and sample DIETENE Diet sheets.

THE DIETENE COMPANY DI 114
3017 Fourth Ave. S., Minneapolis 8, Minn.

I would like to examine the Dietene Diet based on DIETENE Reducing Supplement. Please send diet sheets and FREE one pound sample of DIETENE.

_____ MD

Address _____

City _____ Zone ____ State _____

HOLIDAY GIFTS OF DISCERNMENT

(The College will mail an appropriate and attractive gift card to the recipient)

Fellowship Pledge, American College of Physicians
$7.50, framed and delivered

A.C.P. FELLOWSHIP PLEDGE

Engraved with artist's outlined initials and the College seal in color; mounted and framed in an official frame, larger but of the same design as the certificate frame. All Fellows subscribe to this pledge at time of induction. The line near the bottom of the pledge is for the signature of the Fellow. For the reception room or office. For Fellows only.

FELLOWSHIP KEY

A charm, bearing the seal of The American College of Physicians; wrought in solid gold and embossed in The College colors. For Fellows only.

Price, including engraving initials and date of election, delivered, $7.50.

SUBSCRIPTION TO "ANNALS OF INTERNAL MEDICINE"

A suitable and stimulating gift for that doctor friend who is not a member of the College. *Special Christmas Rate, $9.00 per annum.*

Send orders to

THE AMERICAN COLLEGE OF PHYSICIANS

4200 PINE STREET, PHILADELPHIA 4, PA.

newest

broad-spectrum antibiotic

*Tetracyn**

Brand of **tetracycline**

is now available on prescription from *Pfizer Laboratories,* Division, Chas. Pfizer & Co., Inc., world's largest producer of antibiotics, discoverers of oxytetracycline and the first to describe the structure of tetracycline, nucleus of modern broad-spectrum antibiotic therapy.

Tetracyn is supplied as Capsules, Tablets, Oral Suspension (chocolate flavored), Pediatric Drops (banana flavored), Intravenous, Intramuscular, Ophthalmic Ointment, and Ointment (topical).

*TRADEMARK

For well-tolerated therapy of such common infections as:

Pneumococcal infections, including pneumonia, with or without bacteremia; streptococcal infections, with or without bacteremia, including follicular tonsillitis, septic sore throat, scarlet fever, pharyngitis, cellulitis, urinary tract infections due to susceptible organisms. and meningitis; many staphylococcal infections, with or without bacteremia, including furunculosis, septicemia, abscesses, impetigo, acute otitis media, ophthalmic infections, susceptible urinary tract infections, bronchopulmonary infections, acute bronchitis, pharyngitis, laryngotracheitis, tracheobronchitis, sinusitis, tonsillitis, otitis media, and osteomyelitis; certain mixed bacterial infections; soft tissue infections due to susceptible organisms.

Pfizer PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.

. . . safe

for the obese, the diabetic and others with caloric restrictions

konsyl *the sugar-free hydrophilic colloid*

konsyl *100% Plantago ovata concentrate without added sugars or other diluents. Available—6 and 12 oz. containers. Samples on request.*

BURTON, PARSONS & COMPANY • Washington 9, D.C.

NIGHT and DAY

patients appreciate the effectiveness of **LUASMIN** in controlling the distressing symptoms of **bronchial asthma . . .**

A capsule and an enteric-coated tablet at bedtime generally results in an uninterrupted **night** of sleep—**and** if needed, capsules give relief during the **day.**

LUASMIN

Enteric Coated Tablets and Capsules

provide

Theophylline Sodium Acetate ..... (3 gr.) 0.2 Gms.
Ephedrine Sulfate ..... (½ gr.) 30 Mg.
Phenobarbital Sodium ..... (½ gr.) 30 Mg.

Also available in half-strength.

For samples just send your Rx blank marked 7-LU-11

Brewer EST. 1852

BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

ILIDAR 'ROCHE'

WELL-TOLERATED VASODILATOR

for relief of aching, numbness, coldness, and blanching of the extremities due to vasospasm

PROPERTIES..... Ilidar relieves vasospasm and increases peripheral circulation by (1) direct vasodilation, and (2) adrenergic blockade, i.e., sympatholysis, adrenolysis, and epinephrine reversal.

INDICATIONS..... Peripheral diseases characterized by vasospasm, e.g., Raynaud's Disease, thromboangiitis obliterans, arteriosclerosis obliterans, endarteritis, postphlebitic syndrome, etc.

CONTRAINDICATIONS..... There are no known absolute contraindications. Use cautiously in the presence of asthma, coronary disease, cardiac decompensation, and peptic ulcer. Transient postural hypotension may result from overdosage.

DOSAGE..... One 25 mg tablet t.i.d., gradually increased as necessary (recommended maximum dosage, 300 mg daily).

HOFFMANN-LA ROCHE INC • ROCHE PARK • NUTLEY 10 • NEW JERSEY

ILIDAR® *Phosphate—brand of azapetine phosphate (6-allyl-6, 7-dihydro-5H-dibenz[c, e]azepine)*

PHOTOGRAPH BY VICTOR KEPPLER

Penicillin—that she can *drink*

PENALEV®

SOLUBLE TABLETS POTASSIUM PENICILLIN G

Readily soluble in milk, fruit juice, infant formulas, PENALEV is a highly agreeable way to give penicillin to your young patients. "The rheumatic child who should receive routine year-round penicillin prophylaxis,"[1] won't object to penicillin when she can drink it.

PENALEV is effective in all infections where oral penicillin is indicated. Its solubility makes it a useful form for regulation of dosage. Convenient for prescription compounding, too.

Quick Information: PENALEV is supplied in soluble tablets of 50,000, 100,000, 200,000, 250,000, 500,000, 1,000,000 units of potassium penicillin G each. Dosage depends on type and severity of the infection.

Reference: 1. J.A.M.A. 151:347, 1953.

In Myocardial Infarction

C·R·P·A*

C-Reactive-Protein Antiserum — Schieffelin

A highly sensitive test for presence of inflammation

- Investigators have found this test to be consistently negative in cases of cardiac insufficiency uncomplicated by myocardial infarction and inflammation.[1,4]
- based upon presence of specific C-reactive protein in serum of patients with certain inflammatory diseases — characteristic precipitin reaction develops upon addition of C·R·P·A to serum of such patients . . . C-reactive protein is never found in normal serum.[2]
- simple, economical, routine laboratory procedure that has been demonstrated to be the most consistently positive test in the presence of rheumatic activity[3] . . . often reveals presence of subclinical inflammatory reactions . . . detects relapse or recurrence of inflammatory disease . . . and aids in gauging adequacy of therapeutic regimens.
- "False positive tests do not occur since CRP is not present, even in trace amounts, in normal sera"[3] . . . accurate qualitative reading may be made within 30 minutes . . . preliminary quantitative estimate obtained within 2 hours.

For detailed instructions on the materials and techniques required for the use of C·R·P·A — Schieffelin, just send us a request and we will mail you a descriptive brochure.

1. Kroop, I. G. and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95 (May) 1954.
2. Wood, H. F., and McCarty, M.: J. Clin. Investigation 30:616 (June) 1951.
3. Stollerman, G. H., et al.: Am. J. Med. 15:645 (Nov.) 1953.
4. Hedlund, P.: Acta med. Scandinav., Supplement 196:579, 1947.

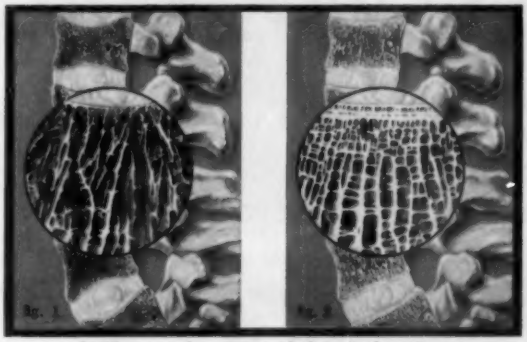
Supplied: 1 cc. vials (30-40 determinations)

Schieffelin & Co., Pharmaceutical and Research Laboratories since 1794

18 Cooper Square, New York 3, N. Y.

*trademark

AGING CHANGES THE BONE PICTURE



lumbar vertebrae, magnified sagittal sections

The vital role that estrogen and androgen play in the preparation and recalcification of bone matrix readily explains why declining sex hormone production which accompanies aging is most frequently the cause of osteoporosis. Note typical atrophic changes characteristic of postmenopausal osteoporosis (fig. 1) in contrast to normal bone matrix (fig. 2). Reifenstein* is of the opinion that some degree of osteoporosis is almost "physiologic" after the menopause, and that clinical osteoporosis may be found in about 10 per cent of women over 50 years of age.

With combined estrogen-androgen therapy, "pain in the spine and other bones is relieved considerably or completely in a matter of weeks to months," and with extended periods of treatment, the prognosis for bone recalcification is good.*

Combining both estrogen and androgen, "Premarin" with Methyltestosterone provides a dual approach for maximum efficiency in treating osteoporosis. A brochure outlining full details of therapy is available at your request.

*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, Philadelphia, The Blakiston Company, 1950, p. 655.

"Premarin" with Methyltestosterone is supplied in two potencies: the *yellow* tablet (No. 879) contains 1.25 mg. of conjugated estrogens equine and 10 mg. of methyltestosterone; the *red* tablet (No. 878) contains 0.625 mg. and 5 mg. respectively. Both potencies are available in bottles of 100 and 1,000 tablets.

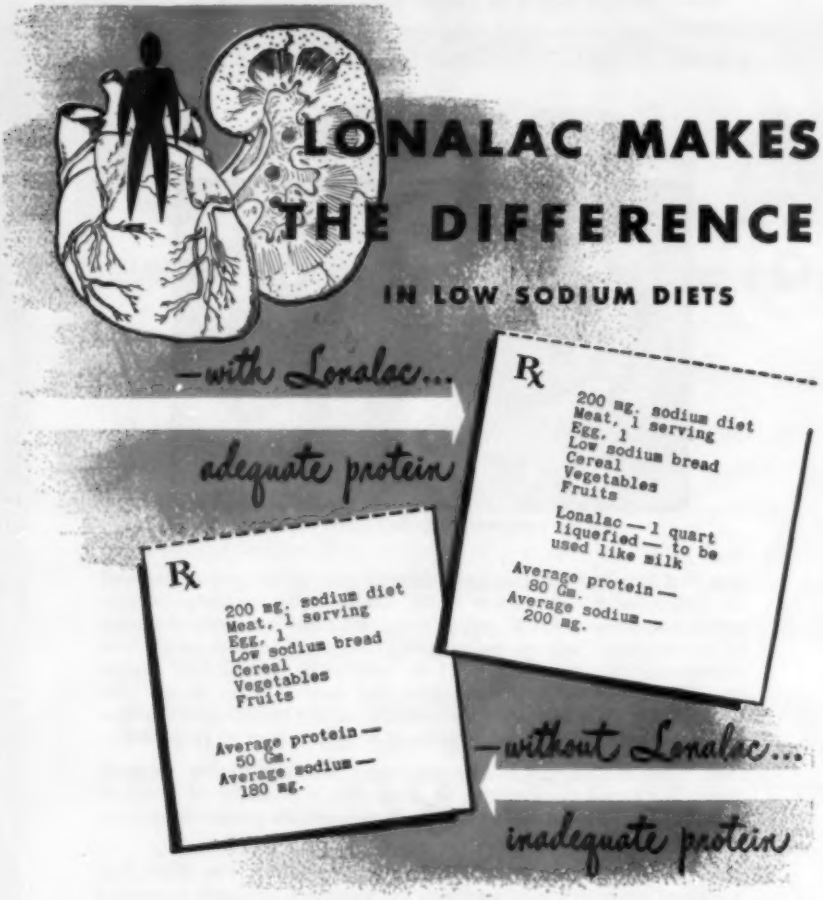
"PREMARIN"® with METHYLTESTOSTERONE

for combined estrogen-androgen therapy

Ayerst

New York, N. Y., Montreal, Canada

5423



Nutritionally similar to whole milk but with negligible sodium content, Lonalac solves the problem created by the high sodium content of the usual protein foods.

When sodium intake must be sharply restricted, protein deficiency is seriously threatened . . . since meat and eggs can be used only in small quantities and milk, with its still higher sodium content, usually must be eliminated.

With Lonalac supplying the protein equivalent of milk, the patient's nutritional needs can be generously met, even on a 200 mg. sodium diet.

Lonalac is used just as milk is used, as a beverage and in soups, muffins, desserts, etc. It permits varied and appetizing meals that encourage patients to adhere to a low sodium regimen.

Lonalac is virtually free of cholesterol.

Lonalac is supplied in 1 pound and economical 4 pound cans. Low sodium diet outlines suitable for use by patients are available on request.

Lonalac

The low sodium, high protein food

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD

"...BEST METHOD AVAILABLE..."

After giving 'Teldrin' *Spansule* capsules to 30 allergic patients over a 6 month period, Rogers[1] concluded:

"It is our belief that this drug in this form provides the best method available for using antihistamine medication."

'Teldrin' *Spansule* capsules are "the best method available" because they incorporate 3 distinct advantages:

1. They contain chlorprophenpyridamine maleate, the widely prescribed, well-tolerated antihistamine.
2. They release this drug slowly, continuously, and uninterruptedly over a period of 8-10 hours, with a therapeutic effect lasting approximately 12 hours. Side effects are thus held to a minimum.
3. They provide maximum dosage convenience.

TELDRIN*

chlorprophenpyridamine maleate

SPANSULE*

brand of sustained release capsules

S.K.F.'s widely acclaimed new

ANTIHISTAMINE

preparation

made only by

Smith, Kline & French Laboratories, Philadelphia 1

the originators of sustained release oral medication

1. Rogers, H. L.: Ann. Allergy 12:266 (May-June) 1954.

★T.M. Reg. U.S. Pat. Off. Patent Applied For

in everyday practice

PENICILLIN
still the antibiotic of first choice for common infections . . .

REINFORCED BY

TRIPLE SULFONAMIDES
to increase antibacterial range and reduce resistance . . .

Three strengths:
125M, 250M, 500M

Each tablet contains:
Penicillin G Potassium, Crystalline 125,000 (or 250,000 or 500,000) units
Sulfadiazine . . . . . 0.167 Gm.
Sulfamerazine . . . . 0.167 Gm.
Sulfamethazine . . . . 0.167 Gm.

Supplied:
Scored tablets in bottles of 50.
Biosulfa 125M also available in bottles of 500.

® TRADEMARK, REG. U. S. PAT. OFF.

Upjohn

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

INDEX TO ADVERTISERS

November, 1954

Abbott Laboratories 37
A.C.P. Holiday Gifts 60
A.I.M. Wanted Back Issues 71
American Bakers Association 14
American Cancer Society, Inc. 56
Ames Company, Inc. 10
Appleton-Century-Crofts, Inc. .. Second Cover
B. F. Ascher & Company, Inc. 38
Ayerst Laboratories 19, 42, 67
Borcherdt Malt Extract Company 6
Brewer & Company, Inc. 63
Briggs Company, The 13
Bristol Laboratories Inc.
Insert facing page 16
Burdick Corporation, The 57
Burroughs Wellcome & Co. (U.S.A.) Inc. 44
Burton, Parsons & Co. 62
Chicago Dietetic Supply House, Inc. 56
Ciba Pharmaceutical Products, Inc., 33, 53, 72
County Surgical Co., Inc. 56
Davies, Rose & Company, Limited 24
Dietene Company, The 59
Eaton Laboratories 11
E. Fougera & Company, Inc. 46
General Electric Company, X-Ray Dept. .. 23
Paul B. Hoeber, Inc. 2
Hoffmann-La Roche Inc.
Insert facing page 32, 64
Irwin, Neisler & Company 20–21, 52
Lea & Febiger 4
Lederle Laboratories Division, American Cyanamid Company 4, 26–27
Eli Lilly and Company ..... Third Cover
Lloyd Brothers, Inc. 40–41
Macmillan Company, The 1
S. E. Massengill Company, The 29, 54
Mead Johnson & Company 8, 47, 68
Medical Protective Company, The 13
Wm. S. Merrell Co., The 22
National Tuberculosis Association 56
Oxford University Press, Inc. 6
Parke, Davis & Company 18
Pfizer Laboratories, Div. of Chas. Pfizer & Co., Inc. 15, 48–49, 61
Pharmacia Laboratories, Inc. 32
Pitman-Moore Company 58
J. B. Roerig and Company 45
William H. Rorer, Inc. 34
Sanborn Company 28
W. B. Saunders Company 3
Schering Corporation 25
Schieffelin & Co. 66
G. D. Searle & Co. 51
Sharp & Dohme, Division of Merck & Co., Inc. 50, 65
Smith, Kline & French Laboratories 16, 30–31, 69
E. R. Squibb & Sons, Division of Mathieson Chemical Corporation 43
University of Pennsylvania Graduate School of Medicine 12
Upjohn Company, The 12–13, 70, 71
Varick Pharmacal Co., Inc. 36
Warner-Chilcott Laboratories, Inc. 7, 9
White Laboratories, Inc. 35
Williams & Wilkins Company, The 5
Winthrop-Stearns Inc. 39
Woodward Medical Personnel Bureau ... 12
Wyeth Laboratories 17, 55

WANTED

Back Issues of

ANNALS OF INTERNAL MEDICINE

Good used copies of the *following* issues are now needed. Only those issues which are currently being advertised will be accepted.

$1.50 each for

Vol.	I, No. 1—July, 1927
Vol.	I, No. 2—August, 1927
Vol.	I, No. 4—October, 1927
Vol.	II, No. 5—November, 1928

$1.00 each for

Vol.	I, No. 5—November, 1927
Vol.	I, No. 6—December, 1927
Vol.	I, No. 7—January, 1928
Vol.	I, No. 8—February, 1928
Vol.	II, No. 1—July, 1928
Vol.	II, No. 4—October, 1928
Vol.	IV, No. 8—February, 1931
Vol.	VI, No. 1—July, 1932
Vol.	VI, No. 4—October, 1932
Vol.	VI, No. 8—February, 1933
Vol.	VII, No. 1—July, 1933

75¢ each for

Vol. XXXIX, No. 3—September, 1953	
Vol. XXXIX, No. 4—October, 1953	

Address Journals to:

E. R. LOVELAND, Executive Secretary
4200 Pine Street
Philadelphia 4, Pa.

in refractory or relapsing cases

ERYTHROMYCIN
the antibiotic of choice
against resistant
Gram-positive cocci . . .

REINFORCED BY

TRIPLE SULFONAMIDES
to cover Gram-negative bacteria
and to potentiate
the erythromycin . . .

Each tablet contains:

Erythromycin	100 mg.
Sulfadiazine	0.083 Gm.
Sulfamerazine	0.083 Gm.
Sulfamethazine	0.083 Gm.

Supplied:
Protection-coated tablets
in bottles of 50 and 500.

®TRADEMARK

Upjohn

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

"complete symptomatic relief" in peptic ulcer patients...

Antrenyl®

In a recent study, patients with acute symptoms of peptic ulcer obtained relief 24 to 36 hours after taking Antrenyl, a potent anti-ulcer agent.

ANTRENYL—prescribed as an adjunct to rest, sedation, antacids and diet—offers the peptic ulcer patient optimal benefits. It is also of value in other conditions marked by gastrointestinal spasm.

ANTRENYL inhibits gastrointestinal motility and gastric secretion. Side effects are either mild or absent, and there is no bitter aftertaste.

ANTRENYL is available as tablets (white, scored), 5 mg.; syrup, 5 mg. per 4-ml. teaspoonful; tablets (peach-colored, scored), 5 mg. with phenobarbital, 15 mg.; Pediatric Drops (with dropper), each drop containing 1 mg. of Antrenyl bromide.

1. ROGERS, M.P., AND GRAY, G.L.: AM. J. DIGEST. DIS. 19:180 (JUNE) 1952.

Antrenyl® bromide (oxyphenonium bromide CIBA)

CIBA
SUMMIT, N. J.

the key

to efficient,

well-tolerated

diuretic therapy

AMPOULES

DICURIN PROCAINE SOLUTION

(Mercathoxylline Procaine, Lilly)

May be given subcutaneously or intramuscularly with no pain or stinging on injection. A stable, ready-to-use mercurial diuretic.

Dose: From 0.5 to 2 cc. daily.

Supplied: In 2-cc. and 10-cc. ampoules.

Order a supply of 'Dicurin Procaine' Solution today from your local pharmacist. You will appreciate its effectiveness and ready-to-use convenience.

ELI LILLY AND COMPANY, INDIANAPOLIS 6, INDIANA, U.S.A.

ANNALS OF INTERNAL MEDICINE

OFFICIAL PERIODICAL OF THE AMERICAN COLLEGE OF PHYSICIANS

EDITOR

MAURICE C. PINCOFFS, M.D., Baltimore

ASSISTANT EDITOR

PAUL W. CLOUGH, M.D., Baltimore

EDITORIAL BOARD

WALTER L. PALMER, M.D., Chicago — ALEX M. BURGESS, SR., M.D., Providence

DAVID P. BARR, M.D., New York — EUGENE B. FERRIS, M.D., Atlanta

O. H. PERRY PEPPER, M.D., Philadelphia

EXECUTIVE SECRETARY

EDWARD R. LOVELAND, Philadelphia

Editorial Office—University Hospital, Baltimore 1, Maryland

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

Place of Publication—Prince & Lemon Sts., Lancaster, Pa.

MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, J. A. M. A. 96: 2006, 1931.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. Selected monographs and books in the field of internal medicine will be reviewed monthly in the ANNALS. Authors and publishers wishing to submit such material should send it to the Editor. Since it is not possible to review all books submitted, a monthly list of all those received will be published in the review section.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscription price per annum, net postpaid: $10.00, United States, Canada, Hawaii, and Puerto Rico; $7.00, in the above countries, to bona fide medical students, interns and residents; $11.00, other countries. Prices for back numbers furnished upon application. Single numbers, current volume, when available, $1.25. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Executive Secretary's Office.

BUSINESS CORRESPONDENCE. All correspondence relating to business matters, advertising, subscriptions to the ANNALS, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

LANCASTER PRESS, INC., LANCASTER, PA.